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Atty. Dkt. No. 071949-5301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jeffrey R. Dahlen, et al.

Title: USE OF B-TYPE NATRIURETIC PEPTIDE AS A PROGNOSTIC INDICATOR IN ACUTE CORONARY SYNDROMES

Appl. No.: 09/835,298

Filing Date: 4/13/2001

Examiner: Lam, Ann Y.

Art Unit: 1641

Confirmation Number: 4762

CERTIFICATE OF MAILING

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Vanessa E. Agha
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Vanessa E. Agha
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3-2-07
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APPEAL BRIEF TRANSMITTAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
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Sir:

Transmitted herewith is an amendment in the above-identified application.

[X] Appeal Brief (29 pages) with sixteen attachments.

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[**X**] The fee required for additional claims is calculated below:

	Claims As Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	16	-	30	=	0	x	$50.00	=	$0.00
Independent Claims:	4	-	6	=	0	x	$200.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$360.00	=	$0.00
							CLAIMS FEE TOTAL	=	$0.00

[ ] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[ ] Extension for response filed within the first month
[ ] Extension for response filed within the second month
[ ] Extension for response filed within the third month
[ ] Extension for response filed within the fourth month
[ ] Extension for response filed within the fifth month

[X]	Appeal Brief Fee	$500.00
	FEE TOTAL:	$500.00
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	TOTAL FEE:	$500.00

A credit card payment form in the amount of $500.00 is enclosed.

The Commissioner is hereby authorized to charge any additional fess which may be required regarding this application under 37 C.F.R. §§1.16-1.17 or 41.20, or credit any overpayment, to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date 03/02/2007

By _____

FOLEY & LARDNER LLP
Customer Number: 30542
Telephone: (858) 847-6722
Facsimile: (858) 792-6773

Richard Warburg, Reg. No. 32,327
By Barry S. Wilson, Reg. No. 39,431
Attorney for Applicant

PATENT
071949-5301

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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APPEAL BRIEF

Mail Stop Appeal Brief - Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants (hereinafter "Appellants") hereby appeal the Final Rejection of claims 23-28, 32-34, and 38. This Appeal Brief is accompanied by a Notice of Appeal. The fee for this Appeal Brief (37 C.F.R. § 41.20(b)(2)) accompanies this filing. If the fee is absent or incorrect or if any additional fees are due in this regard, please charge or credit our Deposit Account No. 50-0872 for the appropriate amount.

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Real Party in Interest

The real party in interest in this appeal is Biosite Incorporated, which is the assignee of the present application.

Related Appeals and Interferences

The present application, filed on April 13, 2001, was the subject of an interference with U.S. Patent 6,461,828 issued to Stanton and Jackowski.

On May 18, 2005, following decision on the preliminary motions filed in the interference, judgment was entered against Stanton and Jackowski. A copy of the preliminary motions decision and the final judgment from the interference is provided herewith in Appendix C of this Brief, as required by 37 C.F.R. § 41.37(c)(1)(x). Following entry of judgment against Stanton and Jackowski in the interference, a formal Notice of Allowance was issued in the present application. Out of an abundance of caution, Appellants filed a Request for Continued Examination so that various publications made of record in the interference could be placed into the present application's file history.

Appellants' Request for Continued Examination initiated a new set of rejections in the present application which included (i) definiteness rejections over language that had been in the claims throughout the period in which the interference was contested and the Notice of Allowance issued, and (ii) an obviousness rejection based upon publications that were of record in the application throughout the period in which the interference was contested and the Notice of Allowance issued. In the Office Action (made final) mailed January 29, 2007, the definiteness rejections are no longer discussed, presumably leaving only the obviousness rejection as the subject of this Appeal.

Appellants note that the subject matter of the present claims (and, indeed, claims that are substantially broader than the claims that are the subject of this Appeal) has been allowed at least three times by the Office -- once when issuing the Stanton and Jackowski patent, and *twice in the present application* (that is, both before and after the interference). Despite these facts, the pending claims stand rejected, and Appellants undertake the present Appeal.

Status of Claims

Claims 1-22 have been cancelled.

Claims 23-38 are pending in the application. For the convenience of the Board, the pending claims are presented in Appendix A of this Brief.

Claims 29-31 and 35-37 have been withdrawn from examination, but remain pending in the application.

Claims 23-28, 32-34, and 38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jackowski, U.S. Patent 5,290,678, in view of Antman *et al.*, *N. Engl. J. Med.* 335: 1342-49 (1996), and further in view of Richards *et al.*, *Heart* 81: 114-120, 1999. This rejection is the subject of this appeal.

Status of Amendments

No amendments or other submissions are pending in the application.

Summary of Claimed Subject Matter

The claimed invention relates to a method for determining a prognosis for a patient suffering from an acute coronary syndrome. As recited in independent claims 23 and 25, the method is directed to "predicting a cardiac mortality rate" for such a patient by performing at least two immunoassays on a patient sample. These immunoassays use at least two antibodies -- one of which binds cardiac Troponin-T or cardiac Troponin-I, and the second of which binds BNP, NT-proBNP or pro-BNP. As recited in independent claims 27 and 33, the method is directed to "assigning a prognosis" to such a patient by performing at least two immunoassays on a patient sample. These immunoassays use at least two antibodies, one of which binds CK-MB, C-reactive protein, cardiac Troponin-T or cardiac Troponin-I, and the second of which binds BNP, NT-proBNP or pro-BNP. In each case, determination of binding to the respective antibodies provides a mechanism to assign a prognosis to the patient.

The term "acute coronary syndromes" ("ACS") refers to a group of coronary disorders that result from ischemic insult to the heart. Patients with ACS form a heterogeneous group, with differences in pathophysiology, clinical presentation, and risk for adverse events. Such patients present to the physician with conditions that span a continuum that includes unstable angina, non-ST-elevation non-Q wave myocardial infarction ("NST"-"MI"), ST-elevation non-Q wave MI, and transmural (Q-wave) MI. Specification, p. 1, ll. 11-20.

It is important to note that "diagnosis" of ACS, which is the ability to distinguish the presence of ACS from its absence, is vastly different from "prognosis," which looks only at those individuals having ACS, and asks which are predisposed to suffer from a variety of subsequent adverse event outcomes. At the worst extreme, workers have estimated that within four to six weeks of presentation with ACS, the risk of death or a subsequent MI is 8-14%. Specification, p. 1, ll. 21-25. The ability to evaluate individuals in order to identify those at the greatest risk of morbidity and mortality can permit caregivers to deliver aggressive treatment to those who can benefit most from that treatment.

With regard to *prognosis*, workers have noted that circulating cardiac troponin levels (troponin is a classic "necrosis" marker that is released when ACS becomes sufficiently severe to cause myocyte death; that is, following the onset of MI) can provide some future risk information. Specification, paragraph bridging p. 1 and 2 (*citing* Antman *et al.*, *N. Eng. J. Med.* 335: 1342-49 (1996), relied upon by the Examiner in the rejection).

Similarly, following the onset of MI, the plasma concentration of BNP has been shown to rise rapidly over the first 24 hours, and then to stabilize; patients with large infarcts may have a second peak in BNP concentration several days later. Workers have also noted that the concentration of BNP measured following an acute MI can provide prognostic information similar to that of necrosis markers such as troponin. Specification, paragraph bridging p. 2 and 3 (*citing*, *inter alia*, Richards *et al.*, *Heart* 81: 114-20 (1999), also relied upon by the Examiner in the rejection; and Arakawa *et al.*, *J. Am. Coll. Cardiol.* 27: 1656-61 (1996)). These previous studies evaluating the prognostic implications of increased BNP concentration were limited to patients with ST-elevation MI. Specification, p. 3, ll. 8-11. This is likely a consequence of the prior art leading the artisan to believe that BNP did not elevate until after the onset of MI, and then in a fashion very similar to traditional necrosis markers such as cardiac troponins.

As noted above, the present claims relate to *combining* BNP (or its closely related markers NT-proBNP and the 108-residue precursor of both BNP and NT-proBNP, see Specification, p. 2, ll. 18-27) with another marker such as a cardiac troponin for use in prognosis of ACS. The present inventors discovered for the first time that BNP was a statistically significant independent *prognostic* marker when combined with necrosis markers such as cardiac troponins. For example, data in the specification demonstrates that increasing BNP

concentration is associated adverse outcomes, even in ACS patients in which troponins have not increased above normal levels. Moreover, this independent association applies across the entire spectrum of ACS, even in the absence of acute MI, and so includes those patients with unstable angina. Specification, p. 12, ll. 20-24 and p. 22 ll. 1-29.

Support for claim 23 is found in the specification, for example, at p. 3, ll. 16-29, at p. 4, ll. 21-28, at p. 8, ll. 13-19, and at p. 14, ll. 11-12; support for claim 24 is found in the specification, for example, at p. 9, ll. 17-18; support for claim 25 is found in the specification, for example, at p. 3, ll. 16-29, at p. 4, ll. 21-28, at p. 8, ll. 13-19, and at p. 14, ll. 11-12; support for claim 26 is found in the specification, for example, at p. 9, ll. 17-18; support for claim 27 is found in the specification, for example, at p. 3, ll. 16-29, at p. 4, ll. 21-28, at p. 8, ll. 13-19, at p. 14, ll. 11-12, at p. 16, l. 22, and at p. 17, l. 15; support for claim 28 is found in the specification, for example, at p. 9, ll. 17-18; support for claim 29 is found in the specification, for example, at p. 7, ll. 20 and 27; support for claim 30 is found in the specification, for example, at p. 7, ll. 7, 12 and 26, and at p. 8, l. 5; support for claim 31 is found in the specification, for example, at p. 8, l. 6; support for claim 32 is found in the specification, for example, at p. 8, l. 6; support for claim 33 is found in the specification, for example, at p. 3, ll. 16-29, at p. 4, ll. 21-28, at p. 8, ll. 13-19, at p. 14, ll. 11-12, at p. 16, l. 22, and at p. 17, l. 15; support for claim 34 is found in the specification, for example, at p. 9, ll. 17-18; support for claim 35 is found in the specification, for example, at p. 7, ll. 20 and 27; support for claim 36 is found in the specification, for example, at p. 7, ll. 7, 12 and 26, and at p. 8, l. 5; support for claim 37 is found in the specification, for example, at p. 8, l. 6; and support for claim 38 is found in the specification, for example, at p. 8, l. 6.

Grounds for Rejection to be Reviewed on Appeal

1. The rejection of claims 23-28, 32-34, and 38 as allegedly being unpatentable over Jackowski, U.S. Patent 5,290,678, in view of Antman *et al.*, *N. Engl. J. Med.* 335: 1342-49 (1996), and further in view of Richards *et al.*, *Heart* 81: 114-20 (1999).

Argument

1. Rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. §103(a)

Appellants request that the rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103(a) be withdrawn or reversed.

The Examiner begins the obviousness analysis with an initial bias – that the primary '678 patent "teaches the invention substantially as claimed." As demonstrated below, the Examiner immediately contradicts this conclusion. But Appellants respectfully submit that this initial bias colors the entire obviousness analysis. In view of this fact, the *prima facie* case of obviousness asserted by the Examiner is fatally flawed from its very inception.

Furthermore, Appellants have provided a showing of secondary considerations as indicia of non-obviousness to address any possible *prima facie* rejection that may have been established. Appellants' showing includes detailed evidence that the claimed invention provides superior results; evidence as to why this feature of the claimed invention was unexpected, and was actually contrary to the teachings of the prior art; evidence of the acclaim that greeted the invention; and evidence of copying and adoption of the invention in the art. Appellants respectfully submit that this evidence concerning objective indicia of nonobviousness is more than sufficient to rebut any *prima facie* case of obviousness that can possibly be established based on the references cited by the Examiner.

A. The Examiner's rationale in rejecting the claims

The Examiner's rationale in rejecting the claims can be found in the Office Action (made final) mailed on January 29, 2007 (hereinafter referred to as "the Office Action").

The Examiner begins with U.S. Patent 5,290,678, issued to Jackowski, as the primary reference in the rejection. The Examiner characterizes the '678 patent as follows: "Jackowski teaches the invention substantially as claimed." Office Action, p. 3, first full paragraph. This statement is followed by a non sequitur: that Jakowski essentially teaches the invention but that "Jackowski does not teach detecting the combination of troponin and BNP, nor for the purpose of detecting cardiac mortality." Office Action, p. 3, second full paragraph. As the claims are directed to the combination of troponin and BNP for the purpose of prognosis, the initial premise that "Jackowski teaches the invention substantially as claimed" clearly cannot be correct.

Given that the Examiner's initial premise is obviously incorrect, the Examiner seeks to combine the primary reference with two secondary references.

One secondary reference is Antman *et al.*, *N. Engl. J. Med.* 335: 1342-49 (1996). According to the last sentence of the Abstract of this publication, "[i]n patients with acute coronary syndromes, cardiac troponin I levels provide useful prognostic information and permit the early identification of patients with an increased risk of death."

The other secondary reference is Richards *et al.*, *Heart* 81: 114-20 (1999). According to the last sentence of the Abstract of this publication, "[p]lasma BNP measured within 1-4 days of acute myocardial infarction is a powerful independent predictor of left ventricular function, heart failure, or death over the subsequent 14 months, and superior to ANF, N-ANF, cGMP, and plasma catecholamines."

The motivation offered to combine the references is stated in the Office Action beginning in the paragraph bridging p. 3 and 4. Basically, the Examiner asserts that it would have been obvious to utilize a multimarker strategy as allegedly taught by Jakowski using cardiac troponin I and BNP "because Antman *et al.* teach that cardiac troponin I in blood is an independent risk factor that identifies patients presenting with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death"; and because "Richards et al. teach that plasma BNP measured within 1 to 4 days of acute myocardial infarction is a powerful independent predictor of death over the subsequent 14 months."

B. The rejection is flawed from its inception due to the Examiner's failure to properly consider the primary reference

As noted above, a clear flaw in the Examiner's understanding of the cited references is readily apparent from the initial premise taken by the Examiner: "Jackowski teaches the invention substantially as claimed." Office Action, p. 3, first full paragraph. The very next paragraph of the Office Action demonstrates the fallacy of this initial premise. Given that the Examiner begins the obviousness analysis with a flawed and clearly biased point of view that the claims are "substantially taught" in a single reference, it is perhaps not surprising that the Examiner concludes that the claims are obvious.

In fact, the primary Jakowski reference which is titled "Diagnostic kit for diagnosing and distinguishing chest pain in early onset thereof" is unrelated to the subject of the present claims

because it is entirely directed to diagnosis of ACS. Diagnosis, which is the ability to distinguish the presence of disease from its absence, is a vastly different issue from "prognosis," which looks only at those individuals having the disease, and asks which are predisposed to suffer from an event of interest at some later time point.

Unlike the subject matter of Jakowski, the present claims are directed to prognosis. Moreover, the present claims require performing assays that detect two markers, one of which is selected from the group consisting of BNP, NT-proBNP, and pro-BNP. Nowhere in Jakowski is BNP, NT-proBNP, or pro-BNP mentioned, or even contemplated.

Although silent on the use of BNP, NT-proBNP, or pro-BNP even for diagnosis, the Jakowski '678 patent discusses other protein biomarkers for diagnosis of myocardial infarction. For example, the '678 patent states that, at the time the patent was filed, "[t]he CK-MB immunoassay is the standard diagnostic test for myocardial infarction." '678 patent, col. 2, ll. 31-32. CK-MB (creatine kinase MB isotype) is a prototypical "cardiac necrosis marker" that is released when myocytes die during myocardial infarction. '678 patent, col. 2, ll. 23-25. CK-MB has certain limitations as an MI diagnostic however, in that it is not released until 6-8 hours after onset of MI, and it is not specific to the heart. '678 patent, col. 2, ll. 59-60, and col. 3, ll. 3-5. The Jakowski '678 patent also mentions that myoglobin is another cardiac necrosis marker, and is believed to be released earlier than CK-MB. '678 patent, col. 3, ll. 11-14. Myoglobin also has characteristics that limit its use as an MI diagnostic. '678 patent, col. 3, ll. 37-50. Similarly, the Jakowski '678 patent discusses cardiac troponin I and cardiac troponin T as cardiac necrosis markers that have the advantage of being somewhat more cardiac specific than CK-MB and myoglobin. '678 patent, col. 4, ll. 22-42.

The '678 patent concludes that a combination of cardiac necrosis markers can be used to improve diagnosis of unstable angina or myocardial infarction:

> The disadvantages of the prior art may be overcome by providing a one-step, accurate, rapid, and portable panel diagnostic test to be used in emergency settings to detect the presence of at least three markers of cardiac damage in a patient's serum. The test results will determine whether the patient is suffering from unstable angina or whether a myocardial infarction has taken place.

'678 patent, col. 5, ll. 17-24. But the '678 patent never discusses or even alludes to the use of any "multimarker strategy" for purposes of prognosis in patients suffering from ACS.

Responding to this criticism of the Examiner's characterization of the primary '678 patent, the Examiner offers a personal opinion: "one of ordinary skill in the art would nevertheless recognize that Jackowski teaches the general concept of a multiple marker approach for determining different medical conditions related to cardiac damage particularly where the markers are released and peak at different times." Office Action, p. 14, first full paragraph. To the extent that the Examiner is asserting that the primary '678 patent teaches anything concerning the use of any "multimarker strategy" for purposes of prognosis, the Examiner's position is only a personal opinion, and is unsupported by any objective evidence. Jakowski describes use of different markers "released and [which] peak at different times" so that the test can diagnose the cardiac injury "at an early stage of cardiac damage," while retaining the ability to "detect MI if the patient arrives for diagnosis many hours after onset of chest pain." How this concept could possibly be relevant to the claimed methods is not explained, either in the art or by the Examiner.

For the foregoing reasons, the initial premise taken by the Examiner in the rejection (that the Jakowski '678 patent teaches the invention substantially as claimed) is unfounded. Nothing in the primary reference even alludes to the use of any "multimarker strategy" for purposes of prognosis in ACS, nor even alludes to the use of BNP, NT-proBNP, or pro-BNP for any purposes whatsoever. Moreover, any alleged motivation to use the "multimarker strategy" disclosed in the '678 patent for purposes of prognosis in ACS results from improper conflation of diagnosis with prognosis and assertions of personal opinion not founded by the evidence.

Appellants respectfully submit that the rejection is based on a flawed foundation, which colors the Examiner's entire approach to analysis of the present claims. This alone renders the rejection fatally flawed.

C. The objective indicia of nonobviousness of the claimed invention require that the claimed invention be found non-obvious

As described in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), the factual underpinnings of any obviousness analysis are: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention at the time of invention, (3) the level of ordinary skill in the art, and (4) the objective indicia of nonobviousness. As discussed in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218

USPQ 871, 879 (Fed. Cir. 1983), the objective indicia "may often be the most probative and cogent evidence [of nonobviousness] in the record." Such objective indicia of nonobviousness can include evidence of unexpected superior results, industry acclaim, and copying and adoption by others.

While the Examiner has not formulated a *prima facie* obviousness rejection, Appellants acknowledge that the two secondary references separately disclose the individual use of cardiac troponin and BNP for prognosis in myocardial infarction, with the caveat that nothing in either secondary publication indicates that cardiac troponins and BNP are independent of one another, or that they should be used together for purposes of prognosis in ACS. Nevertheless, if one assumes for the sake of argument that the present rejection somehow constitutes a *prima facie* case of obviousness, the evidence of record demonstrating the superior unexpected results of the present invention, industry acclaim, and copying and adoption by others rebuts any such *prima facie* case and demonstrates that the claimed invention is, in fact, non-obvious.

The present specification provides data demonstrating that BNP concentrations measured in ACS patients provides information on which individuals are significantly more likely to suffer death, a future myocardial infarction, or new or progressing congestive heart failure. *See, e.g.*, specification, p. 23, first full paragraph. Importantly, the prognostic information provided by BNP was demonstrated to be independent of the prognostic information provided by cardiac troponin. These data demonstrate that, for example, even in individuals having increased troponin concentrations, BNP concentrations provide additional information on which individuals are significantly more likely to suffer from an adverse outcome. Specification, paragraph bridging p. 22 and 23. Thus, the results obtained by combining BNP and cardiac troponin measurements for prognosis in ACS are superior to the results obtained using either measurement alone. *See, e.g.*, Declaration of Dr. Norman Paradis, paragraph 10.

The superior properties of combining BNP and cardiac troponin for prognosis in ACS described in the present specification were later confirmed in the scientific literature. For example, shortly after the filing date of the present application, the data and conclusions contained in the present application were published in the *New England Journal of Medicine,* perhaps the preeminent medical journal in the world. *Compare, e.g.*, Figures 1-4 of de Lemos *et*

al., N. Engl. J. Med. 345: 1014-21 (2001) to Figures 1-4 of the present specification. As taught in the present specification and confirmed through subsequent publication in the prestigious *NEJM*, the present inventors discovered that BNP measurements and cardiac troponin measurements provide independent prognostic information in ACS patients (*see e.g.*, specification, p. 13, first full paragraph).

In fact, Appellants' discovery was considered so important and so unexpected that it was not only deemed worthy of publication in the *NEJM*, but the *NEJM*'s editors also published an Editorial in the same *NEJM* issue, emphasizing the importance of the discovery to its readers:

> Use of the clinical characteristics of the patient, the electrocardiographic findings, and the levels of traditional serum markers of myocyte necrosis, such as the creatine kinase MB fraction and troponin I, is only partially successful in risk stratification. In patients who have unstable angina or myocardial infarction without ST-segment elevation, an elevated troponin level confers an increased short-term risk of death. However, as compared with data from cohort studies, data from clinical trials reveal that the troponin level has less prognostic value. One recent study demonstrated that the measurement of three markers of myocyte necrosis — troponin I, creatine kinase MB, and myoglobin — significantly increased physicians' ability to detect acute coronary syndromes, as compared with the use of each marker alone. However, a patient who has unstable angina but no evidence of myocyte necrosis still has underlying rupture or erosion of plaques and may still have an increased risk of cardiac events.
>
> As our understanding of the pathophysiology of the acute coronary syndromes advances, our ability to stratify patients according to risk improves in tandem. This issue of the *Journal* contains two articles — one by de Lemos et al. and one by Bayes-Genis et al. — on important new markers for use in risk stratification for acute coronary syndromes based on neurohormonal activation and inflammation. De Lemos and colleagues measured plasma levels of brain (B-type) natriuretic peptide, a natriuretic and vasodilative peptide regulated by ventricular wall tension and stored mainly in the ventricular myocardium, in 2525 patients with acute coronary syndromes. A single measurement of B-type natriuretic peptide obtained a median of 40 hours after the onset of ischemic symptoms predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, or unstable angina, as well as the risk of new or progressive congestive heart failure and new or recurrent myocardial infarction. Moreover, the relation between the long-term risk of death and the B-type natriuretic peptide level was independent of electrocardiographic changes, troponin I levels, renal function, and the presence or absence of clinical evidence of congestive heart failure. Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the

> basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

Rabbani, *N. Engl. J. Med.* 345: 1057-59 (2001) (emphasis added). As discussed by Dr. Paradis in his declaration at paragraph 6, the artisan understands that the *NEJM* is reserved for discoveries of the highest medical importance. And companion editorials are generally reserved to highlight findings that are extremely important, even by the already high *NEJM* standards. This is clear evidence of the acclaim that greeted publication of Appellants' data in the scientific literature.

Moreover, within less than one year of the publication of this data from the present application in *NEJM*, other researchers published a similar article concerning the biosynthetically related polypeptide NT-proBNP, demonstrating that NT-proBNP and cardiac troponin measurements also provide independent prognostic information in ACS, and stating that BNP and NT-proBNP are "remarkably similar" in this regard. *See*, Omland *et al.*, *Circulation* 106: 2913-18 (2002).

Additionally, Dr. Paradis notes in paragraph 10 of his declaration that Sabatine *et al.*, *Circulation* 105: 1760-63, 2002, reports on the use of BNP, cardiac troponin I, and an inflammatory marker (C-reactive protein, or CRP) in a "multimarker strategy" for risk stratification of ACS patients. Dr. Paradis also refers to Silver *et al.*, "BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Disease," *CHF* 10[5 Suppl. 3]: 1-30 (2004). In this report, prepared by "an expert panel . . . gathered by selecting clinicians and scientists with expertise with the natriuretic peptide system," the acceptance and practical advantage of combined measurements of BNP and cardiac troponin is made clear (emphasis added):

> 7.2 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Multimarker panels that include BNP troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes.

The publications by Omland *et al.*, Sabatine *et al.*, and the BNP Consensus Panel 2004 are clear evidence of copying and adoption of the claimed invention in the art. *See also*, Paradis declaration, paragraph 10.

Appellants note that the comparative data in the specification which illustrates the claimed invention must be considered in reaching a conclusion with regard to the obviousness of the claims. MPEP § 716.01(a). In addition, the publications referred to above are further evidence that the comparative data is correct, accepted, and adopted in the art, and must be considered. MPEP § 716.02(g).

When the evidence is properly considered in its entirety, it is clear that the combination of BNP and cardiac troponin measurements for prognosis in ACS provides superior properties compared to the art of record. Furthermore, Appellants invention was met with acclaim and was quickly copied and adopted within the art. The evidence supporting secondary considerations of acclimation and copying is more than sufficient to rebut any *prima facie* case of obviousness that may have been established.

D. The superior properties of the claimed invention were unexpected and of substantial practical advantage

Prior to Appellants' discovery, the art lead the skilled artisan to erroneously believe that BNP (and the related peptides such as NT-proBNP) would at best provide similar information to cardiac necrosis markers such as troponin, and so would not provide independent information as demonstrated by the Appellants. Thus, it was unexpected and surprising that BNP measurements and cardiac necrosis markers such as cardiac troponin measurements would provide independent prognostic information in acute coronary syndromes, such that when combined, would provide an improved ability to stratify risk in ACS patients in comparison to either BNP or cardiac troponin alone. Additionally, it was unexpected that BNP measurements and cardiac troponin measurements would provide independent prognostic information across the entire spectrum of ACS conditions, as the art led one to believe that any information provided by BNP would be restricted to the subset of acute myocardial infarction.

As discussed in detail by Dr. Norman Alan Paradis in his declaration, it was understood in the art that cardiac troponins are markers of cardiac necrosis – that is, cardiac troponins are

increased in myocardial infarction "presumably because the amount of cardiac necrosis increases." Paradis declaration, paragraph 5, quoting from Antman *et al.* Prior to the present discovery, Hassan and co-workers reported in *Médecine Nucléaire* 24: 301-10 (2000) that BNP is similar to cardiac troponins, in that BNP also increases due to necrosis. Specifically, Hassan *et al.* describes the use of thallium-201 single photon emission computerized tomography (Tl-201 SPECT) to distinguish subjects having *necrotic* myocardium from subjects having *ischemic* myocardium but no necrosis. Hassan *et al.* examined plasma BNP concentrations in these two groups, and concluded that BNP was significantly increased in the case of cardiac necrosis. On the other hand, Hassan concluded that BNP did not increase due to cardiac ischemia. Paradis declaration, paragraph 5.

These publications would lead the skilled artisan to conclude that BNP, like cardiac troponin, is nothing more than a marker of cardiac necrosis, and would be elevated only after the onset of MI. Moreover, because BNP, like troponin, would increase "presumably because the amount of cardiac necrosis increases," the skilled artisan would conclude that BNP, to the extent it provided prognostic information, would be similar to necrosis markers like that of cardiac troponin. Paradis declaration, paragraph 5.

Such a conclusion is consistent with the prior art generally. For example, Arakawa *et al.*, JACC 27: 1656-61, 1996, entitled "Plasma brain natriuretic peptide concentrations predict survival after acute myocardial infarction" (cited in an IDS submitted October 31, 2005) states the following on p. 1660 (emphasis added):

> 1) [I]t has been shown that hypoxia is an independent stimulus for brain natriuretic peptide release, suggesting that myocardial ischemia stimulates the release of brain natriuretic peptide; 2) because the increase in plasma brain natriuretic peptide after myocardial infarction is closely related to infarct size, brain natriuretic peptide, like cardiac enzymes or macromolecules, may be released from the infarcted or border area between the infarcted and noninfarcted areas. The observation that brain natriuretic peptide mRNA is expressed in ventricular tissue more rapidly than atrial natriuretic peptide mRNA in the rat myocardial infarction model suggests that brain natriuretic peptide production may be immediately increased by the changes in ventricular function that occur after myocardial damage or myocardial ischemia. Thus, after myocardial infarction, cardiac production and release of brain natriuretic peptide may be immediately accelerated, in contrast to atrial natriuretic peptide, and plasma brain

> natriuretic peptide level may indicate the severity of left ventricular dysfunction and myocardial damage.

The quoted text states that plasma BNP is increased after myocardial infarction, and that cardiac production and release of BNP is accelerated after myocardial infarction and after myocardial ischemia. Moreover, this excerpt from the Arakawa *et al.* publication also notes that BNP may be released from infarcted tissues in the same manner as cardiac troponin ("brain natriuretic peptide, like cardiac enzymes or macromolecules, may be released from the infarcted or border area between the infarcted and noninfarcted areas").

Both Hassan *et al.* and Arakawa *et al.* are also consistent with the Richards *et al.* publication (cited by the Examiner in the rejection and published after Arakawa *et al.*), which looks at BNP levels only in subjects having an acute MI. *See*, Richards *et al.*, p. 114, last full paragraph and last partial paragraph.

Each of Hassan *et al.*, Arakawa *et al.*, and Richards *et al.*, would inform the artisan that BNP is a necrosis marker, and should perform like other such markers, including cardiac troponin. Furthermore, the prior art would suggest to the artisan that BNP and cardiac troponin would not be independent markers, since each are released from infarcted tissues in a similar fashion. *See* Paradis declaration, paragraphs 7-9. As demonstrated in the present specification, such a conclusion is incorrect.

The practical importance of discovering that BNP and cardiac troponin measurements provide independent prognostic information in ACS is that the combined markers provide an improved prognosis of ACS patients. Again, as Dr. Paradis notes, this practical advantage has been widely lauded, acknowledged, and adopted in the art, as demonstrated by the Rabbani editorial accompanying publication of Appellants' data in the *NEJM,* and by the excerpt from Silver *et al.*, "BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Disease," *CHF* 10[5 Suppl. 3]: 1-30, 2004, quoted above.

Furthermore, the present invention is applicable not just in acute myocardial infarction, but also "provides powerful risk-stratification across the entire spectrum of acute coronary

syndromes," including for example unstable angina (a disease not generally regarded as involving necrosis). Specification, p. 12, last full paragraph. By way of contrast, the prior art discusses above, and particularly the Hassan *et al.* article, would suggest to the artisan that BNP would not provide information in ACS conditions other than acute myocardial infarction, as BNP would not be elevated except after necrosis had occurred.

While the prior art focuses on an ST-elevation myocardial infarction population, the present invention reports for the first time that BNP is an independent prognostic marker, relative to cardiac troponins, across the entire spectrum of ACS conditions including conditions such as myocardial infarction without ST-segment elevation and unstable angina. Specification, p. 21, first paragraph. As discussed by Dr. Paradis in paragraphs 7 and 8 of his declaration, this feature of the present invention was again of such significance that its publication warranted special mention in the Rabbani *NEJM* editorial:

> A single measurement of B-type natriuretic peptide obtained a median of 40 hours after the onset of ischemic symptoms predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, or unstable angina, as well as the risk of new or progressive congestive heart failure and new or recurrent myocardial infarction.... Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

That the claimed invention can provide prognostic information across the entire spectrum of acute coronary syndromes was unexpected, because the scientific literature at the time indicated that BNP elevated only after myocardial necrosis, and so measurements would not be applicable outside of the context of acute myocardial infarction. Given the teaching in the prior art that BNP would not be increased outside of the context of acute myocardial infarction, Dr. Paradis concludes that one of ordinary skill was surprised to learn that BNP is an independent prognostic marker, relative to cardiac troponins, even in ACS conditions such as unstable angina. Paradis declaration, paragraph 9.

Again, these results are of a significant practical advantage, as the combined markers provide a more effective tool for identifying patients at increased risk for clinically important cardiac events. These superior and unexpected properties of the claimed invention, and the

secondary considerations represented by the widespread approval and adoption of the claimed invention in the art, rebut any *prima facie* case of obviousness that may have been established by the Examiner. *See, e.g.*, MPEP § 716.02(a).

E. The Examiner's responses to Appellants' evidence of objective indicia of nonobviousness evince a failure to carefully consider the evidence of record

Appellants have discussed in detail the evidence, in the form of data, provided in the present specification demonstrating that the claimed invention provides superior results because the prognostic information provided by BNP is independent of the prognostic information provided by cardiac troponin. Appellants have also presented, in the form of a declaration by Dr. Paradis, a detailed discussion as to why this feature of the claimed invention was unexpected, and was actually contrary to the teachings of the prior art, which informed the artisan that BNP is a classic necrosis marker and should perform like other such markers, including cardiac troponin. Appellants have also presented evidence of the acclaim that greeted the invention (in the form of the Rabbani editorial) and copying and adoption of the invention (in the form of the Sabatine *et al.*, *Circulation* publication and the BNP Consensus Panel 2004 excerpt). Appellants respectfully submit that this evidence concerning these objective indicia of nonobviousness rebuts any *prima facie* case of obviousness that can possibly be established.

In the Office Action, the Examiner had an opportunity to consider and respond to Appellants' evidence concerning these objective indicia of nonobviousness. The Examiner's remarks in this regard demonstrate a lack of understanding of the art, a failure to carefully consider Appellants' evidence, or both.

In reply to this evidence, the Examiner states "Applicants have not provided evidence as to what was expected" (Office Action, p. 22, ll. 13-14) and "there is no indication in any of the cited references that BNP would provide similar information to troponin" (*id.*, p. 20, ll. 3-5). Given the Paradis declaration, the teachings of the prior art itself, and the acclaim and acceptance that immediately followed publication of Appellants' data in the scientific literature, this statement by the Examiner is baffling, and can only be considered to represent either a lack of understanding of the art or a failure to carefully the evidence of record.

Moreover, the Examiner's assertion that the discussion of the prior art in the Paradis declaration "does not support that it is expected that BNP and troponin I would provide the same prognosis in terms of short-term or long-term risk of death, nor the risk of death during any length of duration" (Office Action, p. 23, ll. 9-12) is the Examiner's personal opinion wholly unsupported by scientific evidence or reasoning that contradicts Dr. Paradis's analysis of the prior art and conclusions drawn therefrom. Dr. Paradis concluded that the prior art informs the artisan that BNP is a classic necrosis marker, and should perform like other such markers, including cardiac troponin. Unlike the Examiner's personal opinion, Dr. Paradis's conclusion is drawn from, and is consistent with, the prior art discussed above, which states that plasma BNP is increased after necrosis occurs, and, as a result, notes that BNP may be released from infarcted tissues in the same manner as cardiac troponin. In view of the objective evidence as a whole, the properties of the claimed invention were both superior and unexpected, notwithstanding the Examiner's personal opinion to the contrary.

The Examiner's remarks also evince a failure to carefully consider the publications on which the Examiner relies. For example, the Examiner states "it is noted that the discovery that troponin I is an independent predictor of death is disclosed by the Antman et al. prior art reference, and the discovery that BNP is an independent predictor of death is disclosed by Richards et al." Office Action, p. 22, ll. 15-18. The Examiner seems to have concluded that the cited articles suggest that troponin I and BNP are independent of one another. Such a conclusion, however, evinces a failure to carefully consider these publications which discuss marker independence in only limited ways; Antman *et al.* indicates that troponin I is independent of CK-MB (*see, e.g.*, Antman *et al.*, p. 1343, section labeled "Statistical Analysis"), while Richards *et al.* indicates that BNP is independent of "clinical features, noradrenaline concentrations, and LVEF [left ventricular ejection fraction]" (*see, e.g.,* Richards *et al.*, p. 118, last paragraph). Neither of these publications even suggest that troponin I and BNP are independent of one another. Had these articles done this, Appellants' invention would not have received the acclaim that it did in the *NEJM*. Indeed, neither of these publications concludes anything at all about a combination of cardiac troponin with BNP.

The Examiner also argues that Appellants' evidence that the prior art indicated that BNP should perform like cardiac troponin "is not persuasive as Richards et al. disclose in Table 1 on

p. 115 that troponin T was also measured [in addition to BNP]" (Office Action, p. 19, ll. 18-19) and that that Richards *et al.* "teach[es] a different time frame in measuring BNP" as compared to that which Antman *et al.* used to evaluate cardiac troponin. The Examiner implies that this would somehow lead the skilled artisan to conclude that BNP would provide independent prognostic information relative to cardiac troponin. Such a conclusion, however, is contrary to the evidence of record.

That troponin T was measured in Richards *et al.* is hardly surprising, as Richards *et al.* reports on an acute MI population, and cardiac troponins are sensitive markers of acute MI. And, indeed, the troponin T data presented in Richards *et al.* confirms that the population under study had suffered from an acute MI. Of far more relevance to the present obviousness analysis is the fact that BNP and troponin were individually known to be markers of poor prognosis after myocardial infarction at least by 1996 (when Arakawa *et al.* and Antman *et al.* were published). Three years later, the Richards *et al.* publication reported data on both cardiac troponin and BNP, and considered the independence of BNP as a prognostic marker to certain other variables. Yet Richards *et al.* did not report that BNP is an independent predictor of adverse outcome relative to cardiac troponin.

So, while the Examiner asserts that it would have been obvious to combine cardiac troponin and BNP measurements for purposes of prognosis, a highly skilled artisan that was well placed to perform such a method apparently did not do so. One possible conclusion is that, based on the understanding in the art at the time, cardiac troponin and BNP were expected to provide similar prognostic information, and so the authors of Richards *et al.* did not see any value in performing such an analysis. Another possible conclusion is that the authors of Richards *et al.* did perform the analysis, but failed to discover that cardiac troponin and BNP were independent prognosis markers. In either case, despite having data on both cardiac troponin and BNP, Richards *et al.*, does not suggest combining these markers as recited in the present claims, and would not lead the skilled artisan to conclude that BNP would provide independent prognostic information relative to cardiac troponin.

Furthermore, while Richards *et al.* only collects samples from patients from 24 to 96 hours after the onset of MI symptoms for BNP measurement, the Examiner simply ignores the

fact that previous workers had demonstrated that BNP is elevated at about the same time as cardiac troponin, and had already inferred from those results that BNP may be released from infarcted tissues in the same manner as cardiac troponin. *See, e.g.*, Arakawa *et al.*, p. 1657, section entitled "Blood sampling and assays" (mean time to first sample collection 6 ± 5 hours after onset of symptoms).

So while the Examiner would focus only on a comparison of Richards *et al.* with Antman *et al.*, the evidence of record should properly be considered as a whole. Considered in the correct light, one is led to Dr. Paradis's conclusion -- that the properties of the claimed invention were both superior and unexpected, a conclusion that is further reinforced by the acclaim and adoption that followed publication of Appellants' data in the scientific literature.

The legal basis for several of the Examiner's rebuttal remarks is lacking. For example, Appellants have provided evidence that BNP provides prognostic information that is independent of cardiac troponin across the entire spectrum of ACS conditions including unstable angina, and that this is provides another unexpected and superior property of the claimed invention. The Examiner states in reply that "these arguments are not directed to the limitations claimed by applicants that are rejected by the Examiner." Office Action, p. 20, ll. 12-21. This statement by the Examiner is again baffling. The claims relate to prognosis in a patient with ACS. Appellants have provided evidence that it was unexpected that the claimed invention could provide superior prognostic information for the entire spectrum of ACS conditions. The fact that the Examiner focuses only on a myocardial infarction population in the rejection does nothing to diminish the relevance of Appellants' evidence of unexpected superior properties.

Similarly, Appellants have noted that Sabatine *et al.*, *Circulation* 105: 1760-63, 2002, which reports on the use of BNP, cardiac troponin I, and CRP in a "multimarker strategy" for risk stratification of ACS patients, confirms the data in the present specification and represents evidence of both copying and adoption by others of the claimed invention. The Examiner responds that Appellants remarks concerning Sabatine *et al.* do not specifically address "prognosis of death." Office Action, sentence bridging p. 23 and 24. Yet even a cursory reading of the Abstract of Sabatine *et al.* reveals that the publication discloses "a near doubling of the mortality risk for each additional biomarker that was elevated." There can be no valid reason for

the Examiner to ignore the evidence simply because Appellants did or did not use some specific phrase in describing Sabatine *et al.*

F. The evidence of record, taken as a whole, compels the conclusion that the claims are non-obvious over the cited art

As described above, the Examiner begins the obviousness analysis with an initial bias -- that the primary '678 patent "teaches the invention substantially as claimed." While the Examiner immediately contradicts this conclusion, Appellants respectfully submit that this initial bias colors the entire obviousness analysis and renders the obviousness rejection fatally flawed from its very inception.

Appellants have also provided detailed evidence that the claimed invention provides superior results because the prognostic information provided by BNP is independent of the prognostic information provided by cardiac troponin. Appellants have also presented evidence as to why this feature of the claimed invention was unexpected, and was actually contrary to the teachings of the prior art, which informed the artisan that BNP is a classic necrosis marker and should perform like other such markers, including cardiac troponin. Appellants further presented evidence of the acclaim that greeted the invention and widespread adoption of the invention in the art. Appellants respectfully submit that this evidence concerning these objective indicia of nonobviousness is more than sufficient to rebut any *prima facie* case of obviousness that can possibly be established based on the references cited by the Examiner.

Appellants therefore request that the rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103(a) be withdrawn or reversed.

2. Conclusion

For the reasons discussed above, Appellant respectfully requests that the rejection of 23-28, 32-34, and 38 be withdrawn or reversed, and that the claims be allowed to issue.

Respectfully submitted,

Date: 03/02/2007

By: _____

FOLEY & LARDNER
P.O. Box 80278
San Diego, CA 92138-0278
(858) 847-6700 (Voice)
(858) 792-6773 (Fax)

Richard J. Warburg. Reg. No. 32,327
By Barry Wilson, Reg. No. 39,431
Attorney for Applicant

Appendix A: Text of the Claims Involved in the Appeal

1-22 (Cancelled)

23. A method for predicting cardiac mortality rate in a patient with an acute coronary syndrome, comprising:

drawing a sample of a body fluid from said patient,

contacting said sample with a first antibody that specifically binds to a first marker selected from the group consisting of cardiac Troponin-T and cardiac Troponin-I;

contacting said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP , NT-proBNP, and pro-BNP;

providing means for determining binding between each of said respective markers and each of said respective antibodies,

whereby said binding provides a means for determining cardiac mortality rate.

24. The method of claim 23, wherein said body fluid is selected from the group consisting of blood, serum, plasma, and urine.

25. A method for predicting cardiac mortality rate in a patient diagnosed with an acute coronary syndrome, comprising:

drawing a sample of a body fluid from said patient,

contacting said sample with a first antibody that specifically binds to a first marker selected from the group consisting of cardiac Troponin-T and cardiac Troponin-I;

contacting said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP , NT-proBNP, and pro-BNP;

providing means for determining binding between each of said respective markers and each of said respective antibodies,

whereby said binding provides a means for determining cardiac mortality rate.

26. The method of claim 25, wherein said body fluid is selected from the group consisting of blood, serum, plasma, and urine.

27. A method for assigning a prognosis to a patient with an acute coronary syndrome, comprising:

performing an assay on a sample obtained from said patient with a first antibody that specifically binds to a first marker selected from the group consisting of CK-MB, C-reactive protein, cardiac Troponin-T, and cardiac Troponin-I;

performing an assay on said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP, NT-proBNP, and pro-BNP;

determining binding between said markers and said respective antibodies; and

relating said binding to said prognosis.

28. The method of claim 27, wherein said sample is a body fluid selected from the group consisting of blood, serum, plasma, and urine.

29. (Withdrawn) The method of claim 27, wherein said prognosis is a subsequent myocardial infarction.

30. (Withdrawn) The method of claim 27, wherein said prognosis is a subsequent onset of angina.

31. (Withdrawn) The method of claim 27, wherein said prognosis is a subsequent onset of congestive heart failure.

32. The method of claim 27, wherein said prognosis is subsequent death.

33. A method for assigning a prognosis to a patient diagnosed with an acute coronary syndrome, comprising:

performing an assay on a sample obtained from said patient with a first antibody that specifically binds to a first marker selected from the group consisting of CK-MB, C-reactive protein, cardiac Troponin-T, and cardiac Troponin-I;

performing an assay on said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP, NT-proBNP, and pro-BNP;

determining binding between said markers and said respective antibodies; and

relating said binding to said prognosis.

34. The method of claim 33, wherein said sample is a body fluid selected from the group consisting of blood, serum, plasma, and urine.

35. (Withdrawn) The method of claim 33, wherein said prognosis is a subsequent myocardial infarction.

36. (Withdrawn) The method of claim 33, wherein said prognosis is a subsequent onset of angina.

37. (Withdrawn) The method of claim 33, wherein said prognosis is a subsequent onset of congestive heart failure.

38. The method of claim 33, wherein said prognosis is subsequent death.

Appendix B: Evidence Appendix

1. Antman *et al.*, N. Engl. J. Med. 335: 1342-49 (1996)

2. Arakawa *et al.*, J. Am. Coll. Cardiol. 27: 1656-61 (1996)

3. de Lemos *et al.*, N. Engl. J. Med. 345: 1014-21 (2001)

4. Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 148 USPQ 459 (1966)

5. Hassan *et al.*, Médecine Nucléaire 24: 301-10 (2000)

6. Omland *et al.*, Circulation 106: 2913-18 (2002)

7. Rabbani, N. Engl. J. Med. 345: 1057-59 (2001)

8. Richards *et al.*, Heart 81: 114-20 (1999)

9. Sabatine *et al.*, Circulation 105: 1760-63 (2002)

10. Silver *et al.*, "BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Disease," CHF 10[5 Suppl. 3]: 1-30 (2004)

11. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)

12. U.S. Patent No. 6,461,828 to Stanton *et al.*

13. U.S. Patent No. 5,290,678 to Jackowski

14. Declaration by Dr. Norman Alan Paradis

Appendix C: Related Proceedings

Interference with U.S. Patent No. 6,461,828 to Stanton and Jackowski

1. Preliminary motions decision
2. Final judgment from the interference

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

◄ Previous Volume 335:1342-1349 October 31, 1996 Number 18 Next ►

Cardiac-Specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes

Elliott M. Antman, M.D., Milenko J. Tanasijevic, M.D., Bruce Thompson, Ph.D., Mark Schactman, M.S., Carolyn H. McCabe, B.S., Christopher P. Cannon, M.D., George A. Fischer, Ph.D., Anthony Y. Fung, M.B., B.S., Christopher Thompson, M.D., Donald Wybenga, M.D., and Eugene Braunwald, M.D.

ABSTRACT

Background In patients with acute coronary syndromes, it is desirable to identify a sensitive serum marker that is closely related to the degree of myocardial damage, provides prognostic information, and can be measured rapidly. We studied the prognostic value of cardiac troponin I levels in patients with unstable angina or non–Q-wave myocardial infarction.

Methods In a multicenter study, blood specimens from 1404 symptomatic patients were analyzed for cardiac troponin I, a serum marker not detected in the blood of healthy persons. The relation between mortality at 42 days and the level of cardiac troponin I in the specimen obtained on enrollment was determined both before and after adjustment for base-line characteristics.

Results The mortality rate at 42 days was significantly higher in the 573 patients with cardiac troponin I levels of at least 0.4 ng per milliliter (21 deaths, or 3.7 percent) than in the 831 patients with cardiac troponin I levels below 0.4 ng per milliliter (8 deaths, or 1.0 percent; P<0.001). There were statistically significant increases in mortality with increasing levels of cardiac troponin I (P<0.001). Each increase of 1 ng per milliliter in the cardiac troponin I level was associated with a significant increase (P = 0.03) in the risk ratio for death after adjustment for the base-line characteristics that were independently predictive of mortality (ST-segment depression and age >65 years).

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Conclusions In patients with acute coronary syndromes, cardiac troponin I levels provide useful prognostic information and permit the early identificati on of patients with an increased risk of death.

Source Information

From the Department of Medicine (E.M.A., C.H.M., C.P.C., E.B.) and the Clinical Laboratories (M.J.T., G.A.F., D.W.), Brigham and Women's Hospital, Boston; the Maryland Medical Research Institute, Baltimore (B.T., M.S.); and the University of British Columbia, Vancouver (A.Y.F., C.T.).

Address reprint requests to Dr. Antman at the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115.

Full Text of this Article

Related Letters:

Cardiac Troponins in Acute Coronary Syndromes
Haft J. I., Saadeh S. A., Stubbs P., Collinson P., Brogan G. X., Hollander J. E., Thode H., Carbajal E. V., Ohman E. M., Califf R. M., Topol E. J., Antman E. M., Tanasijevic M. J., Cannon C. P., Van de Werf F.
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Plasma Brain Natriuretic Peptide Concentrations Predict Survival After Acute Myocardial Infarction

NAOSHI ARAKAWA, MD, MOTOYUKI NAKAMURA, MD, HIDEHIKO AOKI, MD, KATSUHIKO HIRAMORI, MD

Morioka, Japan

Objectives. This study sought to examine whether plasma brain natriuretic peptide levels can predict prognosis after myocardial infarction.

Background. It has been suggested that concentrations of plasma brain natriuretic peptide reflect left ventricular function. Although the prognosis after myocardial infarction depends on residual left ventricular function, it is not known whether plasma levels of brain natriuretic peptide after the onset of myocardial infarction can be used to predict long-term outcome.

Methods. Plasma brain natriuretic peptide and atrial natriuretic peptide levels as well as invasive hemodynamic variables were measured in 70 patients with acute myocardial infarction (53 men, 17 women; mean age 65 years). Measurements were obtained on admission (mean 6 h after onset) and on day 2 after onset. Mean follow-up period was 18 months.

Results. Plasma brain natriuretic peptide levels measured on admission and day 2 correlated significantly with hemodynamic variables, which are influenced by left ventricular function. However, plasma atrial natriuretic peptide levels correlated with none of the hemodynamic variables measured on admission; and of those measured on day 2, plasma atrial natriuretic peptide levels correlated only with left atrial filling pressure. During the follow-up period (mean 18 ± 7 months), 11 patients died of cardiac causes. By Kaplan-Meier analysis, it was found that patients with plasma brain natriuretic peptide levels higher than the median level, both on admission and on day 2, had significantly higher mortality rates than those with the submedian level (on admission, $p < 0.01$; on day 2, $p < 0.05$). However, only the plasma atrial natriuretic peptide level obtained immediately after admission was significantly related to survival ($p < 0.01$). By Cox proportional hazards model analysis of the noninvasive variables, it was found that plasma brain natriuretic peptide concentration was more closely related to survival after myocardial infarction ($p = 0.0001$).

Conclusions. Increased plasma brain natriuretic peptide concentrations in the early or subacute phase of myocardial infarction are a powerful noninvasive indicator of poor prognosis, possibly reflecting residual left ventricular function after myocardial infarction.

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Brain natriuretic peptide and atrial natriuretic peptide have similar biologic activities. They induce diuresis, natriuresis, vasorelaxation and inhibition of the renin-angiotensin-aldosterone system in both the healthy (1–4) and diseased conditions (5–10). However, the principal sites where these natriuretic peptides are synthesized may be different, that of brain natriuretic peptide being in the ventricular cardiomyocyte (11–13) and that of atrial natriuretic peptide in the atrium (14–16). Plasma concentrations of both brain natriuretic peptide and atrial natriuretic peptide are reported to be increased according to the severity of chronic congestive heart failure (12,17–20). Plasma brain natriuretic peptide concentration may reflect left ventricular function in various cardiac diseases (21–24). In acute myocardial infarction, plasma brain natriuretic peptide level is thought to increase as left ventricular dysfunction progresses (25,26). Because prognosis after myocardial infarction is known to depend on residual left ventricular function (27,28), plasma brain natriuretic peptide concentration may be useful in predicting a prognosis after myocardial infarction.

Plasma atrial natriuretic peptide level has been used in predicting a prognosis after myocardial infarction (29–32). However, the sampling time-points for measuring plasma atrial natriuretic peptide varied: within 12 h (29), from 12 to 24 h (31), or 3 days (30,32) after onset. We demonstrated previously that plasma brain natriuretic peptide level is significantly increased from 12 h through 48 h after the onset of myocardial infarction, whereas plasma atrial natriuretic peptide level did not change significantly (33). Thus, in the present study, we used two different sampling time-points: on admission and on day 2 after onset. We compared the prognostic value of plasma brain natriuretic peptide measurements with those of atrial natriuretic peptide in patients with acute myocardial infarction.

Methods

Subjects. From January 1992 to March 1993, 70 consecutive patients (53 men, 17 women; mean age 65 ± 12 years)

From the Second Department of Internal Medicine, Iwate Medical University, Morioka, Japan.

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Address for correspondence: Dr. Motoyuki Nakamura, Second Department of Internal Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate, 020, Japan.

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admitted to our hospital coronary care unit within 12 h of onset were subjects of the present study. Patients with cardiogenic shock or renal failure (serum creatinine >1.5 mg/dl), or both, were excluded from this study. The diagnosis of myocardial infarction was based on a history of typical chest pain, typical electrocardiographic changes and an increase in serum creatine kinase level. Based on electrocardiographic criteria, the site of infarction was anterior in 32 patients, inferior in 27 patients and at other locations in 11 patients. Fifty-two patients were admitted to the hospital within 6 h of onset, and these patients received coronary reperfusion therapy. Coronary intervention was chosen randomly according to the separate treatment protocols in our coronary care unit (infusion of tissue plasminogen activator, n = 30; emergency percutaneous transluminal coronary angioplasty, n = 22). Eighteen patients were admitted from 6 to 12 h after onset and received only conventional treatment (that is, nitrate and lidocaine). The study was approved by the ethics committee of our hospital, and informed consent was obtained from all patients.

Blood sampling and assays. Immediately after admission (mean, 6 ± 5 h after onset) and on day 2 after onset, blood was withdrawn from a forearm vein for measurement of plasma brain natriuretic peptide and atrial natriuretic peptide concentrations. Blood samples were collected into tubes containing 10 mg of EDTA-2Na and 2,500 U of aprotinin, centrifuged immediately (3,000 rpm at 4°C), and then stored at −80°C until they were analyzed. Plasma levels of brain natriuretic peptide and atrial natriuretic peptide were determined using a commercial radioimmunoassay kit (brain natriuretic peptide, Peninsula Laboratories; atrial natriuretic peptide, Amersham) after extraction using a Sep-Pak C-18 column (Waters Chromatography Division, Millipore) as described in our previous reports (10,34). These assays were performed in duplicate. The minimum detectable level of brain natriuretic peptide was less than 1.7 pg per tube, and cross-reactivity with human atrial natriuretic peptide was less than 0.01%. The intraassay and interassay coefficients of variation for brain natriuretic peptide assays were 12% and 19%, respectively. In our laboratory, mean plasma levels of atrial natriuretic peptide and brain natriuretic peptide in age-matched healthy subjects with no evidence of myocardial ischemia were 29 ± 15 pg/ml (n = 17) and 18 ± 6 pg/ml (n = 13), respectively.

Hemodynamic variables. Pulmonary capillary wedge pressure and cardiac output were measured using a Swan-Ganz catheter (Baxter Corp., Edwards Division) immediately after admission and on day 2 after onset in all patients. Left ventricular ejection fraction and left ventricular end-diastolic pressure were determined during ventricular catheterization in patients treated with reperfusion therapy at the time of admission. The clinical characteristics of the patients grouped according to the median plasma level of brain natriuretic peptide on admission are summarized in Table 1. Coronary reperfusion for acute phase of myocardial infarction was successful in all patients who had received the therapy.

Statistical analysis. Patient survival was assessed either to the day of death or to March 31, 1994. To assess the relation between brain natriuretic peptide and atrial natriuretic peptide and mortality rate, median values were used as a cutoff point; and the Kaplan-Meier method was used to examine the survival rate in each group. The significance of the difference between survival curves was tested by the log-rank test. The chi-square test was used to evaluate the differences in baseline characteristics between groups. Unpaired *t* tests were used to compare mean values between groups. Linear regression analysis was used to assess the relation between plasma levels of natriuretic peptides and hemodynamic variables. The prognostic value of the variables was tested in a Cox proportional hazards regression analysis using the program in the PHREG Procedure (SAS/STAT software). Predictors of survival were obtained by forward stepwise selection model. Data are expressed as mean ± SD. A level of $p < 0.05$ was accepted as statistically significant.

Table 1. Comparison of Clinical, Hemodynamic and Biochemical Variables Grouped According to Median Plasma Level of Brain Natriuretic Peptide on Admission

Variable	BNP ≤59 pg/ml (n = 32)	BNP >59 pg/ml (n = 38)	p Value
No. of deaths	0	11	
Clinical			
Age (yr)	59 ± 10	70 ± 11	< 0.001
M/F	26/6	27/11	NS
Previous MI	1	11	< 0.01
Hypertension	19	24	NS
Angina pectoris	17	25	NS
Anterior MI	10	22	< 0.05
Pulmonary congestion	3	15	< 0.01
Reperfusion therapy	24	28	NS
Medication	9	7	NS
Hemodynamic			
HR (beats/min)	76 ± 10	80 ± 19	NS
SBP (mm Hg)	132 ± 20	111 ± 25	< 0.001
PCWP (mm Hg)	11 ± 5	16 ± 6	< 0.001
CI (liters/min per m^2)	3.3 ± 0.6	2.7 ± 0.8	< 0.001
LVEF (%) (n = 55)	55 ± 10 (n = 28)	47 ± 12 (n = 27)	< 0.05
LVEDP (mm Hg) (n = 55)	16 ± 5 (n = 28)	19 ± 9 (n = 27)	NS
Biochemical			
Max CK (IU/liter)	3,032 ± 4,300	3,325 ± 2,887	NS
Plasma ANP (pg/ml)	98 ± 113	125 ± 79	NS

Data presented are mean value ± SD or number of patients. ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; CI = cardiac index; CK = creatine kinase; F = female; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; M = male; Medication = beta-blockers, angiotensin-converting enzyme inhibitors; MI = myocardial infarction; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

Results

The mean follow-up period was 18 months (range 2 days to 27 months), and the follow-up rate was 100%. Eleven patients died due to cardiac causes during the follow-up period, 7

Table 2. Correlation Coefficients for Hemodynamic Variables and Plasma Natriuretic Peptide Levels in Acute Phase of Myocardial Infarction

	PCWP	CI	SV	LVEF	LVEDP
On Admission					
BNP	0.44*	0.46*	0.44*	−0.42*	0.31*
ANP	0.22	−0.21	−0.07	0.12	0.01
On day 2					
BNP	0.34*	−0.42*	−0.47*		
ANP	0.35*	−0.18	−0.16		

*$p < 0.05$. SV = stroke volume; other abbreviations as in Table 1.

patients died due to refractory heart failure, 2 patients died due to cardiac free-wall rupture during hospitalization, and 2 patients died suddenly after discharge from our hospital.

Plasma natriuretic peptide levels and hemodynamic data. Table 2 shows the correlation coefficients for hemodynamic variables and plasma natriuretic peptides levels on admission and on day 2 after onset. On admission and on day 2, plasma brain natriuretic peptide concentrations correlated significantly with the hemodynamic variables measured at the corresponding time point (pulmonary capillary wedge pressure: on admission, $r = 0.44$, on day 2, $r = 0.34$; cardiac index: on admission, $r = -0.46$, on day 2, $r = -0.42$; stroke volume: on admission, $r = -0.44$, on day 2, $r = -0.47$; left ventricular ejection fraction: on admission, $r = -0.42$; left ventricular end diastolic pressure: on admission, $r = 0.31$, all $p < 0.05$). Plasma atrial natriuretic peptide concentration, in contrast, showed a correlation only with pulmonary capillary wedge pressure and only on day 2 ($r = 0.35$, $p < 0.05$).

Plasma natriuretic peptide levels and clinical outcome. Plasma brain natriuretic peptide concentrations in the patients who died were significantly higher than in those who survived at both sampling time points (on admission: 176 ± 98 vs. 70 ± 58 pg/ml, $p < 0.0001$; on day 2: 125 ± 78 vs. 52 ± 45 pg/ml, $p < 0.0001$). Plasma atrial natriuretic peptide concentrations were also significantly higher in the patients who died than in those who survived (on admission: 170 ± 54 vs. 102 ± 99 pg/ml, $p < 0.05$; on day 2: 138 ± 72 vs. 82 ± 90 pg/ml, $p < 0.05$). The correlation between plasma brain natriuretic peptide and atrial natriuretic peptide levels at corresponding time-points was weak (on admission: $r = 0.30$, $p < 0.05$; on day 2: $r = 0.24$, $p < 0.05$).

Plasma natriuretic peptide levels and survival curve. Figures 1 and 2 depict the Kaplan-Meier survival curves. The patients are divided into two groups according to the median plasma concentrations of brain natriuretic peptide and atrial natriuretic peptide. Figure 1 shows the results for brain natriuretic peptide: the groups with elevated plasma brain natriuretic peptide level on admission (>59 pg/ml) and on day 2 (>43 pg/ml) showed significantly higher mortality rates ($p < 0.01$, $p < 0.05$, respectively). Figure 2 shows the results for atrial natriuretic peptide: the group with higher plasma atrial natriuretic peptide level on admission (>80 pg/ml) showed a significantly higher mortality rate ($p < 0.01$), but the survival curves for day 2 plasma atrial natriuretic peptide levels did not differ significantly.

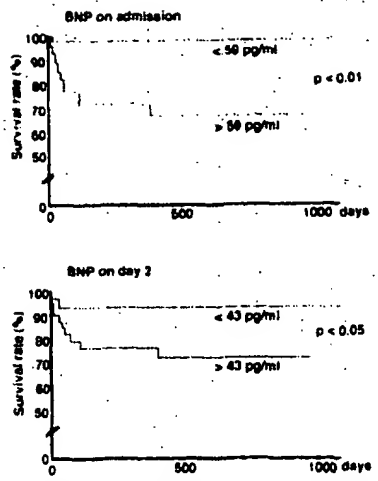

Figure 1. Kaplan-Meier analysis of cumulative survival rate in patients with acute myocardial infarction classified into two groups according to the median value of brain natriuretic peptide (BNP) concentrations on admission (top) and on day 2 (bottom).

To determine if plasma brain natriuretic peptide level was associated with cardiac death caused by congestive heart failure, we examined the survival rate of all subjects excluding patients with sudden cardiac death (n = 2) and cardiac rupture (n = 2). We found that plasma brain natriuretic peptide level had a similar prognostic value for predicting cardiac death due to refractory congestive heart failure.

Using a univariate Cox proportional hazards model, we found that plasma brain natriuretic peptide concentrations on

Figure 2. Kaplan-Meier analysis of cumulative survival rate in patients with acute myocardial infarction classified into two groups according to the median value of atrial natriuretic peptide (ANP) concentrations on admission (top) and on day 2 (bottom).

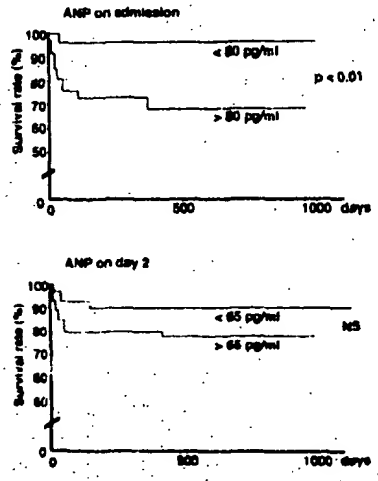

Table 3. Univariate Relations Between Selected Variables and Survival After Myocardial Infarction According to a Cox Proportional Hazards Model

Variable	Chi-Square	p Value
ANP on admission	3.93177	0.0474
BNP on admission	16.18948	0.0001
ANP on day 2	3.33955	0.0676
BNP on day 2	15.44217	0.0001
Maximal CK	0.22802	0.6330
Age	12.71720	0.0004
Gender	0.11084	0.7392
HR	1.14117	0.2854
PCWP	8.24654	0.0041
CI	16.30285	0.0001
SBP	8.63696	0.0033
Pulmonary congestion	10.54013	0.0012
MI site	0.07437	0.7851
Reperfusion therapy	0.40968	0.5221
Angina pectoris	1.49864	0.2209
Hypertension	3.51846	0.0607
Previous MI	3.31751	0.0688

Abbreviations as in Table 1.

admission and on day 2 were also significantly related to survival. Table 3 summarizes the relations between biochemical, hemodynamic and clinical variables and survival after myocardial infarction. Furthermore, according to a multivariate Cox proportional-hazards model, of the noninvasive variables, plasma brain natriuretic peptide concentration on admission was the significant and the most important noninvasive predictor of outcome ($p = 0.0001$, Table 4).

Receiver operating characteristic curve. We examined the sensitivity and specificity of various cutoff values of plasma brain natriuretic peptide and atrial natriuretic peptide levels on admission for predicting survival. A receiver operating characteristic curve was constructed. The curve plotted by the plasma brain natriuretic peptide level on admission was a better predictor than the model based on the plasma atrial natriuretic peptide level on admission (Fig. 3).

Discussion

Several recent reports have demonstrated that plasma atrial natriuretic peptide levels in the acute and subacute phases of myocardial infarction are a good predictor of survival (29–32). However, to our knowledge, our study is the first to report a relation between plasma brain natriuretic peptide level and prognosis after myocardial infarction. We have demonstrated that plasma brain natriuretic peptide concentration in the acute and subacute phases of myocardial infarction is a powerful predictor of long-term outcome and a useful noninvasive marker for identifying the risk of cardiac death. Moreover, plasma brain natriuretic peptide level is more useful as a predictor of survival after myocardial infarction than plasma atrial natriuretic peptide level.

Table 4. Multivariate Relations Between Selected Variables and Survival After Myocardial Infarction According to a Cox Proportional Hazards Model

Variable	Chi-Square	p Value
BNP on admission	21.0347	0.0001
Age	5.4428	0.0196
SBP	2.5948	0.1072
ANP on admission	0.1707	0.6794
Pulmonary congestion	0.7848	0.3757

Abbreviations as in Table 1.

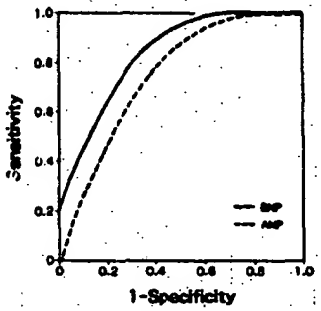

Figure 3. Receiver operating characteristic curves for brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) predicting cardiac death. The true-positive rates (sensitivity) and false-positive rates (1 – specificity) are plotted for various natriuretic peptide cutoff values predicting cardiac death during the follow-up period.

Brain natriuretic peptide and hemodynamic variables. In the present study, plasma brain natriuretic peptide concentrations in the acute and subacute phases of myocardial infarction correlated significantly with pulmonary capillary wedge pressure, cardiac index, stroke volume, left ventricular ejection fraction and left ventricular end-diastolic pressure. These findings are consistent with reports by Mukoyama and coworkers that showed that plasma brain natriuretic peptide concentration correlated significantly with left ventricular function values (25,26). Moreover, Motwani et al. (35) demonstrated that increases in plasma brain natriuretic peptide levels at both early and late stages of myocardial infarction were good indicators of alteration in left ventricular function after treatment with angiotensin-converting enzyme inhibitor. These data suggest that plasma brain natriuretic peptide level is influenced by left ventricular function.

Previous studies. We have found that in the acute and subacute phases of myocardial infarction, the relation between plasma atrial natriuretic peptide concentration and hemodynamic variables was not as strong as that of plasma brain natriuretic peptide. In patients with chronic heart failure, plasma atrial natriuretic peptide level appears to be a good indicator of atrial pressure or pulmonary capillary wedge pressure (cardiac filling pressure) (19,23,36). However, in the acute phase of myocardial infarction, the relation between plasma atrial natriuretic peptide level and intracardiac pres-

sure is not clear. It has been demonstrated that plasma atrial natriuretic peptide concentration after myocardial infarction correlates significantly with cardiac index and intracardiac filling pressure (37–39). Other reports have indicated that there is no significant relation between plasma atrial natriuretic peptide concentration and hemodynamic variables in the acute phase of myocardial infarction (40,41). The reason for this discrepancy is not clear, but there are several possible explanations.

First, massive release of atrial natriuretic peptide from atrial tissue into the circulation immediately after myocardial infarction could lead to depletion of atrial natriuretic peptide stores. Thus, plasma atrial natriuretic peptide concentration would decrease transiently without significant hemodynamic changes occurring (40,42). Second, myocardial infarction complicated by tachyarrhythmia may cause an increase in plasma atrial natriuretic peptide concentration (43). Third, there are reports that thrombolytic therapy in the acute phase of myocardial infarction decreases plasma atrial natriuretic peptide concentration (41,44). Last, in the isolated perfused rat heart, a decrease in coronary flow reduces cardiac atrial natriuretic peptide release (45). These possibilities suggest that plasma atrial natriuretic peptide level may not correlate directly with changes in the hemodynamic values associated with left ventricular dysfunction in patients with acute myocardial infarction.

Mechanisms of brain natriuretic peptide release. In isolated perfused rat hearts, stretching by intraventricular balloon inflation is an independent factor to stimulate brain natriuretic peptide release (46). In patients with chronic heart failure caused by dilated cardiomyopathy, plasma brain natriuretic peptide concentration correlated significantly with left ventricular end-diastolic pressure (21,23). In patients with hypertrophic cardiomyopathy characterized by left ventricular pressure overload, plasma brain natriuretic peptide level increased more than plasma atrial natriuretic peptide level (47). We have previously reported that plasma brain natriuretic peptide concentration correlated significantly with left ventricular end-diastolic pressure but not with left atrial pressure in patients with mitral stenosis (34). These findings indicate that, after myocardial infarction, the increase in ventricular wall stress/tension may be an important factor in stimulating brain natriuretic peptide synthesis and release from ventricular cardiomyocytes.

Two additional mechanisms may stimulate brain natriuretic peptide release in patients with acute myocardial infarction: 1) it has been shown that hypoxia is an independent stimulus for brain natriuretic peptide release (48), suggesting that myocardial ischemia stimulates the release of brain natriuretic peptide; 2) because the increase in plasma brain natriuretic peptide concentration after myocardial infarction is closely related to infarct size (33), brain natriuretic peptide, like cardiac enzymes or macromolecules, may be released from the infarcted or border area between the infarcted and noninfarcted areas. The observation that brain natriuretic peptide mRNA is expressed in ventricular tissue more rapidly than atrial natriuretic peptide mRNA in the rat myocardial infarction model (49) suggests that brain natriuretic peptide production may be immediately increased by the changes in ventricular function that occur after myocardial damage or myocardial ischemia. Thus, after myocardial infarction, cardiac production and release of brain natriuretic peptide may be immediately accelerated, in contrast to atrial natriuretic peptide, and plasma brain natriuretic peptide level may indicate the severity of left ventricular dysfunction and myocardial damage.

Study limitations. Various coronary interventions were used in the acute stage of myocardial infarction in this study. These differences in treatment may have affected prognosis. However, there was no difference in coronary interventions between the two groups classified by plasma brain natriuretic peptide level on admission (Table 1). No significant differences in the subsequent survival rate were found among the variations of coronary interventions in the acute phase of myocardial infarction in the present study group. Moreover, presence of angina pectoris before onset, history of previous myocardial infarction and difference in infarction site did not affect survival rate in the small number of our subjects. The effect of drug treatment (that is, angiotensin-converting enzyme inhibitors, beta-receptor blockers) after myocardial infarction was not assessed in the present study. However, because few patients were given angiotensin-converting enzyme inhibitors ($n = 5$) or beta-blockers ($n = 11$), there was no difference between the two groups. These medications, therefore, may not have significantly biased the results of the present study.

Conclusions. In this study, we found that plasma brain natriuretic peptide level reflects left ventricular function more directly than plasma atrial natriuretic peptide level does. Increased plasma brain natriuretic peptide concentration was significantly related to mortality. We suggest that measurement of plasma brain natriuretic peptide level in the early phase of myocardial infarction may be a useful noninvasive method for identifying individuals at high risk of cardiac death after myocardial infarction.

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THE PROGNOSTIC VALUE OF B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE CORONARY SYNDROMES

JAMES A. DE LEMOS, M.D., DAVID A. MORROW, M.D., M.P.H., JANE H. BENTLEY, B.Sc., TORBJØRN OMLAND, M.D., PH.D., M.P.H., MARC S. SABATINE, M.D., CAROLYN H. MCCABE, B.S., CHRISTIAN HALL, M.D., PH.D., CHRISTOPHER P. CANNON, M.D., AND EUGENE BRAUNWALD, M.D.

ABSTRACT

Background Brain (B-type) natriuretic peptide is a neurohormone synthesized predominantly in ventricular myocardium. Although the circulating level of this neurohormone has been shown to provide independent prognostic information in patients with transmural myocardial infarction, few data are available for patients with acute coronary syndromes in the absence of ST-segment elevation.

Methods We measured B-type natriuretic peptide in plasma specimens obtained a mean (±SD) of 40±20 hours after the onset of ischemic symptoms in 2525 patients from the Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis in Myocardial Infarction 16 study.

Results The base-line level of B-type natriuretic peptide was correlated with the risk of death, heart failure, and myocardial infarction at 30 days and 10 months. The unadjusted rate of death increased in a stepwise fashion among patients in increasing quartiles of base-line B-type natriuretic peptide levels ($P<0.001$). This association remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation ($P=0.02$), patients who had myocardial infarction without ST-segment elevation ($P<0.001$), and patients who had unstable angina ($P<0.001$). After adjustment for independent predictors of the long-term risk of death, the odds ratios for death at 10 months in the second, third, and fourth quartiles of B-type natriuretic peptide were 3.8 (95 percent confidence interval, 1.1 to 13.3), 4.0 (95 percent confidence interval, 1.2 to 13.7), and 5.8 (95 percent confidence interval, 1.7 to 19.7). The level of B-type natriuretic peptide was also associated with the risk of new or recurrent myocardial infarction ($P=0.01$) and new or worsening heart failure ($P<0.001$) at 10 months.

Conclusions A single measurement of B-type natriuretic peptide, obtained in the first few days after the onset of ischemic symptoms, provides predictive information for use in risk stratification across the spectrum of acute coronary syndromes. Cardiac neurohormonal activation may be a unifying feature among patients at high risk for death after acute coronary syndromes. (N Engl J Med 2001;345:1014-21.)

BRAIN (B-type) natriuretic peptide is a 32-amino-acid neurohormone synthesized in ventricular myocardium and released into the circulation in response to ventricular dilatation and pressure overload.[1-3] The actions of this peptide, like those of atrial (A-type) natriuretic peptide, include natriuresis, vasodilatation, inhibition of the renin–angiotensin–aldosterone axis, and inhibition of sympathetic nerve activity.[4] The plasma level of B-type natriuretic peptide is elevated in patients with congestive heart failure and increases in proportion to the degree of left ventricular dysfunction and the severity of symptoms of heart failure.[2,5] After acute myocardial infarction, levels of B-type natriuretic peptide rise rapidly during the first 24 hours and then tend to stabilize.[6-9] Measurement of the level of B-type natriuretic peptide between one and four days after a transmural infarction provides prognostic information that is independent of the left ventricular ejection fraction and other important base-line variables.[8,10-14]

Studies evaluating the prognostic implications of B-type natriuretic peptide have been limited to patients with myocardial infarction with ST-segment elevation, and few data are available on patients who have acute coronary syndromes in the absence of ST-segment elevation. Patients with acute coronary syndromes are a heterogeneous group, with differences in pathophysiology, clinical presentation, and the risk of adverse events. We sought to evaluate the prognostic implications of cardiac neurohormonal activation, as reflected by the plasma level of B-type natriuretic peptide, across the entire spectrum of acute coronary syndromes.

METHODS

Study Population

The Oral Glycoprotein IIb/IIIa Inhibition with Orbofiban in Patients with Unstable Coronary Syndromes–Thrombolysis in Myocardial Infarction 16 trial was a randomized, multicenter trial comparing an oral platelet glycoprotein IIb/IIIa receptor inhibitor, or-

From the Thrombolysis in Myocardial Infarction Study Group, Boston (J.A.D., D.A.M., M.S.S., C.H.M., C.P.C., E.B.); the Donald W. Reynolds Cardiovascular Clinical Research Center, University of Texas, Southwestern Medical School, Dallas (J.A.D.); the Cardiovascular Division and Department of Medicine, Brigham and Women's Hospital, Boston (D.A.M., M.S.S., C.H.M., C.P.C., E.B.); the Nottingham Clinical Research Group, Nottingham, United Kingdom (J.H.B.); and the Research Institute for Internal Medicine, National Hospital, University of Oslo, Oslo, Norway (T.O., C.H.). Address reprint requests to Dr. de Lemos at UT Southwestern Medical Center, 5323 Harry Hines Blvd., Rm. CS7.142, Dallas, TX 75390-9047, or at james.delemos@utsouthwestern.edu.

bofiban, with placebo in 10,288 patients with acute coronary syndromes. The study protocol was approved by the institutional review board of each participating hospital, and all patients provided written informed consent. Patients were included if they presented within 72 hours after the onset of ischemic discomfort and met one or more of the following criteria: electrocardiographic changes (ST-segment depression or elevation of at least 0.5 mm, T-wave inversion of at least 3 mm in at least three leads, or left bundle-branch block), elevated levels of cardiac markers, a history of coronary disease, or an age of at least 65 years in patients with diabetes or vascular disease.[15] Patients received 150 to 162 mg of aspirin daily and were randomly assigned to receive 50 mg of orbofiban twice daily; 50 mg of orbofiban twice daily for one month, followed by 30 mg of orbofiban twice daily; or placebo. The study was terminated prematurely because of an increase in mortality in the group assigned to receive 50 mg twice daily initially and then 30 mg twice daily.[15] The present substudy included all 2525 patients who were assigned to the group given 50 mg of orbofiban twice daily and who provided a base-line plasma specimen suitable for analysis. The data were collected and retained by the study investigators, who also performed the analyses.

Blood Sampling

At the time of enrollment, blood specimens were collected in citrate-treated tubes and centrifuged for at least 12 minutes. The plasma component was frozen and shipped on dry ice to Children's Hospital (Boston), where samples were stored at −70°C. In 925 patients, C-reactive protein was measured with use of a high-sensitivity assay (N Latex CRP assay, Dade Behring, Newark, Del.) and fibrinogen was measured with use of a commercial assay on a BN II analyzer (Dade Behring). After the trial was completed, all available plasma specimens from the group given 50 mg of orbofiban twice daily were shipped to Biosite Diagnostics (San Diego, Calif.), where they were thawed and analyzed.

Biochemical Analyses

Sequential sandwich immunoassays for the quantification of B-type natriuretic peptide and troponin I were performed in 384-well microtiter plates with use of an automated system (Tecan Genesis robotic sample processor 200/8, Durham, N.C.). The amount of analyte was quantified on the basis of the level of binding of alkaline phosphatase–conjugated antibody. The analytic sensitivity of the B-type natriuretic peptide and troponin I immunoassays were approximately 5 pg per milliliter and 50 pg per milliliter, respectively.

End Points

The end points of death from any cause and nonfatal myocardial infarction were evaluated at 30 days and the end of the follow-up period (10 months). Myocardial infarction was defined according to previously reported criteria,[16] and all cases of suspected infarction were adjudicated by a clinical-events committee. Information on the end point of new or worsening heart failure or cardiogenic shock was collected from the case-record forms.

Statistical Analysis

Patients were divided into quartiles on the basis of their B-type natriuretic peptide level at the time of enrollment. The mean values and proportions of base-line variables were compared among quartiles with the use of linear regression for continuous variables and log-linear analysis for categorical variables. The correlation between B-type natriuretic peptide levels and other continuous base-line variables was assessed with the use of Pearson's product-moment correlation coefficient. B-type natriuretic peptide levels were not adjusted for age.

To evaluate its association with clinical outcomes, B-type natriuretic peptide was considered as both a continuous and a categorical variable. The level of B-type natriuretic peptide was compared between patients who met a study end point and those who did not with use of the Wilcoxon rank-sum test. Cox regression analysis was used to evaluate the association between the quartile of B-type natriuretic peptide and the risk of adverse outcomes for the first 30 days after randomization and at 10 months. Stratified analyses were performed among patients with various troponin I levels, as well as those with and those without a clinical diagnosis of heart failure. Analyses were performed in subgroups defined according to the index diagnosis. The quartile ranges were recalculated for each of these subgroups.

For the end point of death from any cause through the end of follow-up (10 months), we constructed a logistic-regression model using forward stepwise selection. Clinical variables for which data were available from more than 75 percent of patients were entered into the model if they had a univariate P value of less than 0.1; variables were removed if they had a multivariate P value greater than or equal to 0.1. Base-line levels of troponin I and B-type natriuretic peptide were then added to the completed model. The final model included only the 2280 patients for whom data were available for all variables. Finally, we performed analyses using the B-type natriuretic peptide threshold of 80 pg per milliliter that has been established for the diagnosis of congestive heart failure.[17]

RESULTS

The study population consisted of 2525 patients: 825 were enrolled after a myocardial infarction with ST-segment elevation, 565 after a myocardial infarction without ST-segment elevation, and 1133 after an episode of unstable angina. In two patients, the index diagnosis was not specified. The B-type natriuretic peptide level ranged from 5 to 1456 pg per milliliter, with a mean (±SD) of 114±126 pg per milliliter, a median of 81 pg per milliliter, and 25th and 75th percentile values of 44 and 138 pg per milliliter, respectively. The mean time from the onset of ischemic symptoms to enrollment was 40±20 hours (median, 40).

Association with Base-Line Clinical Variables

In univariate analyses, higher base-line levels of B-type natriuretic peptide were associated with older age, female sex, white race, and a history of hypertension, heart failure, and vascular disease; the level of B-type natriuretic peptide was inversely associated with a history of hypercholesterolemia and current smoking (Table 1). Patients with higher B-type natriuretic peptide levels were more likely than those with lower levels to present in Killip class II, III, or IV and to have electrocardiographic changes at base line, elevated levels of creatine kinase MB, and renal insufficiency (Table 1). There was no consistent relation between the level of B-type natriuretic peptide and the time from the onset of ischemic symptoms: the median levels were 72, 87, and 81 pg per milliliter for patients presenting less than 24 hours, 24 to 48 hours, and more than 48 hours after the onset of symptoms, respectively.

Although statistically significant, the associations between levels of B-type natriuretic peptide and C-reactive protein levels ($r=0.2$, $P<0.001$), fibrinogen levels ($r=0.18$, $P<0.001$), peak levels of the MB isoform of creatine kinase ($r=0.09$, $P<0.001$), and the ejection fraction ($r=0.23$, $P<0.001$) were only moderately strong. Patients with higher B-type natriuretic peptide levels had a greater number of coronary ar-

TABLE 1. BASE-LINE CLINICAL CHARACTERISTICS ACCORDING TO THE QUARTILE OF B-TYPE NATRIURETIC PEPTIDE LEVEL.*

CHARACTERISTIC†	QUARTILE 1 (5.0–43.6 pg/ml)	QUARTILE 2 (43.7–81.2 pg/ml)	QUARTILE 3 (81.3–137.8 pg/ml)	QUARTILE 4 (137.9–1456.6 pg/ml)	P VALUE FOR TREND
No. of patients	631	632	632	630	
Age — yr	57±10	59±11	61±12	66±11	<0.001
Male sex — no. (%)	474 (75)	465 (74)	472 (75)	405 (64)	<0.001
White race — no. (%)	575 (91)	592 (94)	605 (96)	603 (96)	<0.001
Medical history — no. (%)					
Hypertension	246 (39)	254 (40)	263 (42)	298 (47)	0.003
Congestive heart failure	26 (4)	28 (4)	26 (4)	56 (9)	<0.001
Coronary artery disease	329 (52)	312 (49)	294 (47)	327 (52)	0.7
Peripheral vascular disease	33 (5)	43 (7)	48 (8)	57 (9)	0.008
Cerebrovascular disease	24 (4)	32 (5)	39 (6)	60 (10)	<0.001
Diabetes	138 (22)	133 (21)	132 (21)	152 (24)	0.4
Hypercholesterolemia	199 (32)	191 (30)	173 (27)	149 (24)	<0.001
Smoking status — no. (%)					<0.001
Current smoker	233 (37)	263 (42)	236 (37)	189 (30)	
Never smoked	193 (31)	161 (26)	185 (29)	254 (40)	
Former smoker	204 (32)	205 (33)	209 (33)	186 (30)	
Index diagnosis — no. (%)					<0.001
Myocardial infarction with ST-segment elevation	141 (22)	189 (30)	231 (37)	264 (42)	
Myocardial infarction without ST-segment elevation	87 (14)	137 (22)	159 (25)	182 (29)	
Unstable angina	402 (64)	306 (48)	241 (38)	184 (29)	
Physical findings					
Systolic blood pressure — mm Hg	130±20	129±19	128±22	129±21	0.3
Killip class II, III, or IV — no. (%)	31 (5)	36 (6)	56 (9)	109 (18)	<0.001
Results of diagnostic tests — no. (%)					
Creatinine clearance ≤90 ml/min	146 (24)	185 (31)	229 (38)	350 (58)	<0.001
Creatine kinase MB >upper limit of normal	212 (58)	308 (72)	349 (79)	388 (86)	<0.001
ST-segment depression ≥0.5 mm	270 (43)	297 (47)	311 (49)	356 (57)	<0.001

*Plus–minus values are means ±SD.

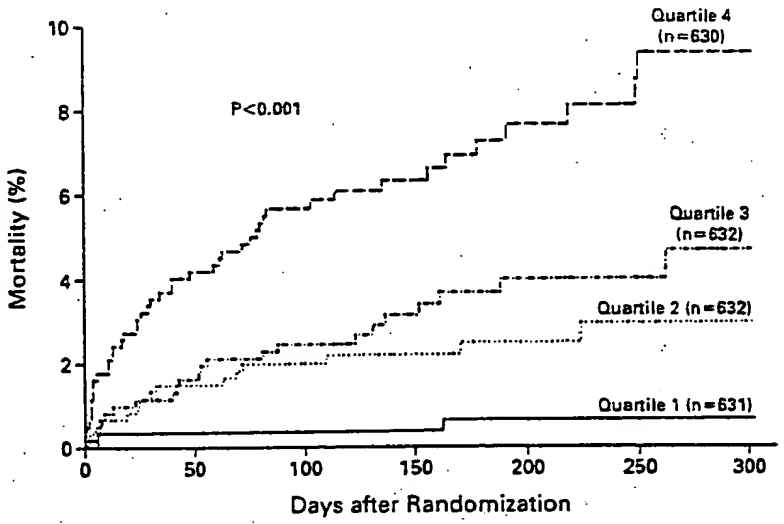
†For each variable, the percentages reflect the total number of patients for whom data were available. In some instances, this number was less than the total number of patients in the quartile.

teries with stenosis of at least 50 percent ($P<0.001$) and a greater likelihood of a positive stress test ($P<0.01$) than patients with lower levels (data not shown).

Clinical Outcomes

The base-line level of B-type natriuretic peptide was higher among patients who died than among those who were alive at 30 days (median, 153 vs. 80 pg per milliliter; $P<0.001$) and at 10 months (median, 143 vs. 79 pg per milliliter; $P<0.001$). These differences remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation ($P=0.002$ at 30 days and $P=0.008$ at 10 months), patients who had myocardial infarction in the absence of ST-segment elevation ($P<0.001$ at both 30 days and 10 months), and patients who had unstable angina ($P=0.002$ at 30 days and $P<0.001$ at 10 months). The level of B-type natriuretic peptide was higher among patients who had new or recurrent myocardial infarction within 30 days ($P=0.02$) or 10 months ($P=0.01$) than among patients who were free of infarction. Finally, the level of B-type natriuretic peptide was higher among patients who had new or worsening heart failure within 30 days ($P<0.001$) or 10 months ($P<0.001$) than among those in whom heart failure did not develop.

The unadjusted mortality rate increased in a stepwise fashion across increasing quartiles of base-line B-type natriuretic peptide levels ($P<0.001$) (Fig. 1). This association remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation, patients who had myocardial infarction in the absence of ST-segment elevation, and patients who had unstable angina (Fig. 2). In addition, the association between the level of B-type natriuretic peptide and the 10-month mortality rate remained graded and significant both among 327 patients with a history of heart failure or a finding of Killip class II, III, or IV at presentation ($P=0.007$) and among 2165 patients without such findings ($P<0.001$). When stratification was based on the level of troponin I at the time of enrollment, increasing levels of B-type natriuretic peptide remained associated with a higher 10-month mortality rate, among both 882 patients with a troponin I level of 0.1 ng per milliliter or less ($P=0.01$) and 1630 patients with a troponin I level



No. at Risk							
Quartile 1	631	615	550	431	321	218	104
Quartile 2	632	603	525	390	283	159	64
Quartile 3	632	615	529	384	266	168	72
Quartile 4	630	594	487	345	227	146	58
Total	2525	2427	2091	1550	1097	691	298

Figure 1. Kaplan–Meier Curves Showing the Cumulative Incidence of Death at 10 Months, According to the Quartile of B-Type Natriuretic Peptide Level at Enrollment.

The range of B-type natriuretic peptide levels was as follows: 5.0 to 43.6 pg per milliliter (quartile 1), 43.7 to 81.2 pg per milliliter (quartile 2), 81.3 to 137.8 pg per milliliter (quartile 3), and 137.9 to 1456.6 pg per milliliter (quartile 4). P<0.001 for the trend among the quartiles.

of more than 0.1 ng per milliliter (P<0.001). Similar results were obtained when stratification was based on troponin I thresholds of 0.4 and 1.5 ng per milliliter (P<0.001 for each comparison of patients above and patients at or below each threshold). The association between B-type natriuretic peptide and mortality at 10 months was significant for both men (P< 0.001) and women (P=0.01).

In a logistic-regression model in which we adjusted for other independent predictors of the long-term risk of death, including age, troponin I levels, and presence or absence of heart failure, renal insufficiency, and ST-segment deviation, increasing levels of B-type natriuretic peptide remained associated with an increased risk of death at 10 months (Fig. 3). The adjusted odds ratios for death at 10 months in the second, third, and fourth quartiles of B-type natriuretic peptide were 3.8 (95 percent confidence interval, 1.1 to 13.3), 4.0 (95 percent confidence interval, 1.2 to 13.7), and 5.8 (95 percent confidence interval, 1.7 to 19.7), respectively (Fig. 3). When age was entered into the model as a continuous variable, the results were unchanged.

Evaluation of a B-Type Natriuretic Peptide Threshold of 80 pg per Milliliter

Patients with a B-type natriuretic peptide level of more than 80 pg per milliliter were significantly more likely to die, have a new or recurrent myocardial infarction, or have new or progressive heart failure than those with a level of 80 pg per milliliter or less (Fig. 4). After adjustment for other independent predictors of the long-term risk of death, a B-type natriuretic peptide level of more than 80 pg per milliliter remained significantly associated with an increased 10-month mortality rate (P=0.04).

DISCUSSION

We have demonstrated in a large, contemporary cohort of patients that a single measurement of B-type natriuretic peptide, obtained a median of 40 hours after the onset of ischemic symptoms, provides powerful information for use in risk stratification across the entire spectrum of acute coronary syndromes. Despite heterogeneity in pathophysiology, clinical presentation, and risk among patients who had myocardial infarction with ST-segment elevation, patients

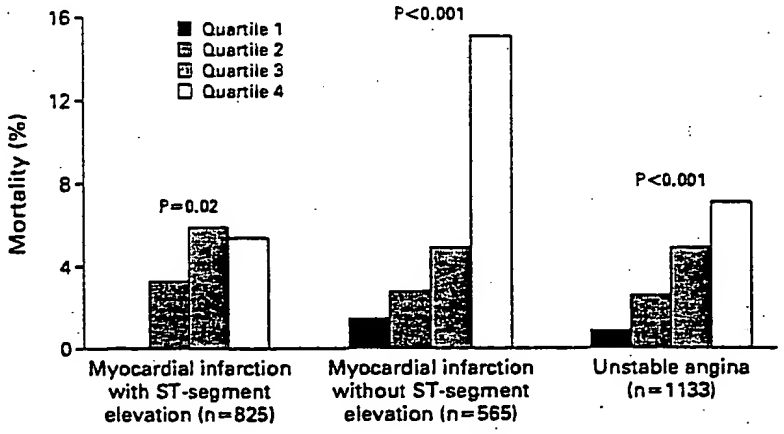


Figure 2. Association between the B-Type Natriuretic Peptide Level and the Mortality Rate at 10 Months, According to the Index Diagnosis.

Quartiles were recalibrated for each of the subgroups. Quartile 1 represents the lowest level of B-type natriuretic peptide, and quartile 4 the highest level. P values are for the trend within each subgroup.

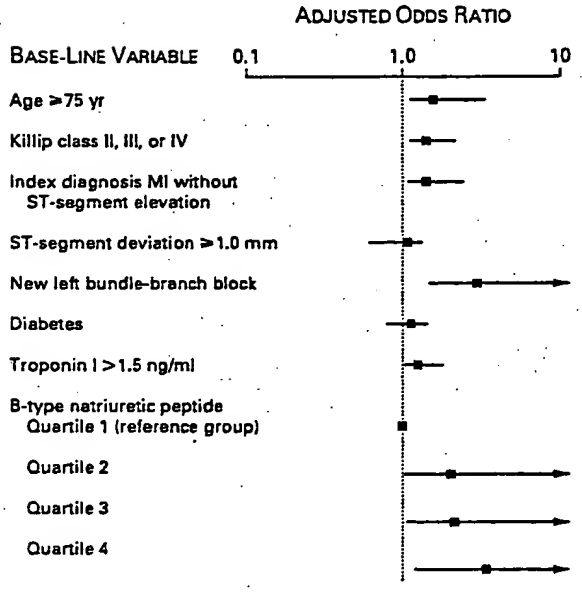


Figure 3. Stepwise Logistic-Regression Model Showing the Association between Selected Base-Line Clinical Variables and the Odds Ratio for Death at 10 Months.

The cardiac troponin I level and B-type natriuretic peptide quartiles were forced into the final model. Horizontal lines are 95 percent confidence intervals. In addition to the variables shown in the figure, the final model included presence or absence of a history of hyperlipidemia, peripheral vascular disease, or heart failure; presence or absence of prior therapy with diuretics, angiotensin-converting–enzyme inhibitors, nitrates, or heparin; heart rate; blood pressure; and creatinine clearance. MI denotes myocardial infarction.

who had myocardial infarction in the absence of ST-segment elevation, and patients who had unstable angina, increasing levels of B-type natriuretic peptide were predictive of an increased risk of death in each of these subgroups. This finding suggests that activation of the cardiac neurohormonal system may be a unifying feature among patients at high risk for death after acute coronary syndromes.

The association between B-type natriuretic peptide and the long-term risk of death was independent of the presence or absence of clinical evidence of heart failure, as well as renal function, the troponin I level, electrocardiographic changes, and other known predictors of the risk of death in patients with acute coronary syndromes. In addition, a high level of B-type natriuretic peptide was associated with an increased risk of nonfatal end points, including new or progressive heart failure and myocardial infarction. Finally, it appears that the previously defined B-type natriuretic peptide threshold of 80 pg per milliliter, indicative of neurohormonal activation in patients with heart failure,[17] is also an appropriate threshold among patients with acute coronary syndromes.

Previous studies have demonstrated that after a myocardial infarction, a higher plasma level of B-type natriuretic peptide is associated with a larger infarct size,[6,18] an increased likelihood of ventricular remodeling,[19] a lower ejection fraction,[11,18] and an increased risk of heart failure and death.[8,10-14] These studies each included fewer than 150 patients and focused on relatively homogeneous groups of patients who had myocardial infarction with ST-segment elevation.

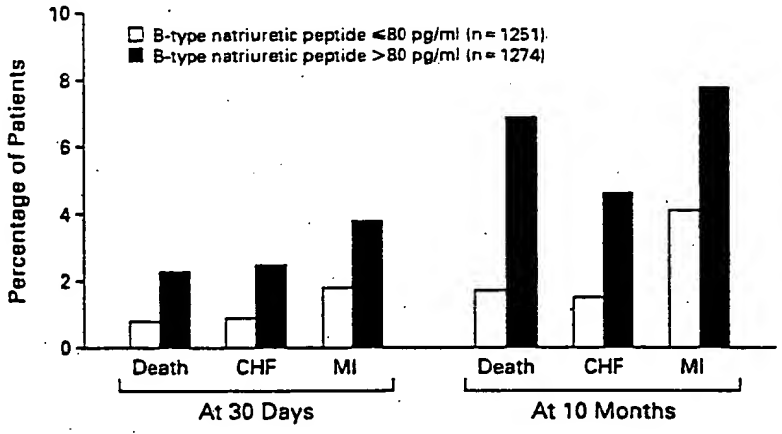


Figure 4. The Incidence of Death, New or Progressive Congestive Heart Failure (CHF), and New or Recurrent Myocardial Infarction (MI) at 30 Days and 10 Months among Patients with B-Type Natriuretic Peptide Levels above or at or below the Prespecified Threshold of 80 pg per Milliliter.

P<0.005 for each comparison.

Our study extends these findings to patients with acute coronary syndromes in the absence of ST-segment elevation, including those with unstable angina and no evidence of myocardial necrosis.

Unlike traditional cardiac biomarkers used to predict risk among patients with acute coronary syndromes, B-type natriuretic peptide has a putative role in the counterregulatory response to ischemia. Therefore, it may act as an index of the extent or severity of the ischemic insult, as well as the degree of underlying impairment in left ventricular function. In an animal model of transmural infarction, the level of expression of the B-type natriuretic peptide gene in the left ventricle was tripled within four hours after coronary ligation, and tissue levels of B-type natriuretic peptide were increased in noninfarcted as well as infarcted regions.[20] The level of B-type natriuretic peptide increases rapidly and transiently after exercise testing in patients with chronic stable angina, and the degree of elevation is correlated with the size of the ischemic territory as measured with the use of nuclear single-photon-emission computed tomography imaging.[21] Furthermore, the level increases transiently after uncomplicated percutaneous transluminal coronary angioplasty, even in the absence of changes in pulmonary-capillary wedge pressure.[22,23]

Several small cross-sectional studies have shown that the level of B-type natriuretic peptide is higher among patients with unstable angina than among patients with stable angina or among healthy controls.[24,25] In one of these studies, a finding of an elevation in B-type natriuretic peptide correlated with echocardiographic findings of regional wall-motion abnormalities, but not with hemodynamic data obtained at the time of simultaneous cardiac catheterization; furthermore, after medical stabilization, wall-motion abnormalities improved and B-type natriuretic peptide levels fell significantly.[25]

Taken together, these findings suggest that myocardial ischemia augments the synthesis and release of B-type natriuretic peptide, even in the absence of myocardial necrosis or preexisting left ventricular dysfunction. Reversible ischemia may transiently increase left ventricular wall stress, which may be sufficient to cause an elevation in B-type natriuretic peptide levels. Our findings further suggest that the prognostic implications of neurohormonal activation are distinct from those of myocyte necrosis; even among patients with unstable angina and those without troponin I elevation, the degree of elevation in B-type natriuretic peptide is of prognostic importance.

We measured B-type natriuretic peptide once, approximately two days after the index event. It is not possible from a single measurement to determine whether neurohormonal activation is reflective of the acute (index) event or of preexisting left ventricular dysfunction. However, even after adjustment for variables such as the presence or absence of a history of hypertension, heart failure, and use of diuretics or angiotensin-converting–enzyme inhibitors, the level of B-type natriuretic peptide remained predictive of the long-term risk of death. A study in patients hospitalized with heart failure suggests that serial measurements of B-type natriuretic peptide may provide more prognostic information than a single measurement, since the prognosis was better when levels fell after therapy than when they remained the same.[26] Future studies should evaluate the use of serial measurements

of B-type natriuretic peptide in patients with acute coronary syndromes.

For a cardiac biomarker to be clinically useful, it must help clinicians select an appropriate therapeutic regimen. For example, patients who have an elevation in troponin T or I levels after acute coronary syndromes appear to derive specific benefit from an early, aggressive strategy that includes potent antiplatelet[27] and antithrombotic[28] therapy and early revascularization.[29] In addition, patients who have elevated C-reactive protein levels after myocardial infarction appear to benefit from statin therapy.[30] Patients with elevated levels of B-type natriuretic peptide after an acute coronary syndrome are at high risk for death, a new myocardial infarction, and heart failure and may benefit from intensive antiplatelet and antithrombotic therapies, neurohormonal antagonism with agents such as beta-blockers and angiotensin-converting–enzyme inhibitors, and early revascularization. Equally important, patients who have normal levels of B-type natriuretic peptide after an acute coronary event appear to have a particularly low long-term risk of death and heart failure. In this group of patients, a less intensive management approach may be appropriate, in order to avoid the cost and risk associated with potentially unnecessary therapies. Future studies should directly assess the role of B-type natriuretic peptide in identifying patients who would benefit from various treatment strategies.

The level of B-type natriuretic peptide, measured in the first few days after an acute coronary event, predicts the long-term risk of death and nonfatal cardiac events across the spectrum of acute coronary syndromes. The prognostic usefulness of B-type natriuretic peptide persists after adjustment for the presence or absence of clinical evidence of heart failure, as well as other important predictors of mortality, including clinical characteristics, renal function, electrocardiographic changes, and troponin I levels. These findings suggest that B-type natriuretic peptide should be measured after an acute coronary syndrome in order to identify patients at high and low risk for adverse outcomes and that treatment, including the intensity of surveillance and the use of aggressive pharmacologic and interventional therapy, should be adjusted accordingly.

Supported in part by grants from Searle (Skokie, Ill.) and Biosite Diagnostics (San Diego, Calif.).

Drs. de Lemos, Morrow, and Omland have received honorariums from Biosite Diagnostics.

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Briefs and Other Related Documents

Supreme Court of the United States
William T. GRAHAM et al., Petitioners,
v.
JOHN DEERE COMPANY OF KANSAS CITY et al.
CALMAR, INC., Petitioner,
v.
COOK CHEMICAL COMPANY.
COLGATE-PALMOLIVE COMPANY, Petitioner,
v.
COOK CHEMICAL COMPANY.
Nos. 11, 37, 43.

Argued Oct. 14, 1965.
Decided Feb. 21, 1966.

In a patent infringement action, the United States District Court for the Western District of Missouri, 216 F.Supp. 272, entered judgment for plaintiffs, and defendants appealed. The Court of Appeals, Eighth Circuit, reversed, 333 F.2d 529. In separate actions, plaintiffs sought declaration that patent was invalid and not infringed. The United States District Court for the Western District of Missouri, 220 F.Supp. 414, held that patent was valid and infringed and plaintiffs appealed. The Court of Appeals, Eighth Circuit, affirmed, 336 F.2d 110. Certiorari was granted in both cases. The Supreme Court, Mr. Justice Clark, held that provision of Patent Act pertaining to nonpatentability of invention because of obviousness was intended to codify judicial precedents embracing principle announced by Supreme Court as early as 1850, that while clear language of provision places emphasis on inquiry into obviousness general level of innovation necessary to sustain patentability remains the same, and that patents at issue were invalid because of obviousness of subject matter.

Judgment in patent infringement action affirmed; judgment in declaratory judgment actions reversed and remanded.

West Headnotes

[1] **Patents ⚿16(1)**
291k16(1) Most Cited Cases
(Formerly 291k16, 291k18)
Provision of Patent Act pertaining to nonpatentability of invention because of obviousness was intended to codify judicial precedents embracing principle announced by Supreme Court as early as 1850; and while clear language of provision places emphasis on inquiry into obviousness, general level of innovation necessary to sustain patentability remains the same. 35 U.S.C.A. § 103.

[2] **Patents ⚿2**
291k2 Most Cited Cases
Federal patent power stems from specific constitutional provision which authorizes Congress to promote progress of useful arts by securing for limited times to inventors exclusive right to their discoveries. U.S.C.A.Const. art. 1, § 8.

[3] **Patents ⚿3**
291k3 Most Cited Cases
Patent clause of Article I of Constitution is both grant of power and limitation. U.S.C.A.Const. art. 1, § 8.

[4] **Patents ⚿3**
291k3 Most Cited Cases
Patent clause of Article I of Constitution is limited to promotion of advances in useful arts. U.S.C.A.Const. art. 1, § 8.

[5] **Patents ⚿2**
291k2 Most Cited Cases
Congress in exercise of patent power may not overreach restraints imposed by stated constitutional purpose to promote advances in useful arts nor may it enlarge patent monopoly without regard to innovation, advancement, or social benefit gained thereby, nor may it authorize issuance of patents whose effects are to remove existent knowledge from public domain or to restrict free access to materials already available. U.S.C.A.Const. art. 1, § 8.

[6] **Patents ⚿16(1)**
291k16(1) Most Cited Cases
(Formerly 291k16)

Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in patent system which by constitutional command must promote progress of useful arts; such is the standard expressed in the Constitution and it may not be ignored. U.S.C.A.Const. art. 1, § 8.

[7] **Patents ⚷16(1)**
291k16(1) Most Cited Cases
(Formerly 291k16)
Patent validity requires reference to standard written into Constitution. U.S.C.A.Const. art. 1, § 8.

[8] **Patents ⚷3**
291k3 Most Cited Cases
Within limits of constitutional grant, Congress may implement stated purpose by selecting policy which in its judgment best effectuates constitutional aim. U.S.C.A.Const. art. 1, § 8.

[9] **Patents ⚷3**
291k3 Most Cited Cases
Congressional power to implement stated purpose of framers with respect to granting of patents by selecting policy which in its judgment best effectuates constitutional aim is but corollary to grant to Congress of any Article I power. U.S.C.A.Const. art. 1, § 8.

[10] **Patents ⚷2**
291k2 Most Cited Cases
Within scope established by Constitution, Congress may set out conditions and tests for patentability. U.S.C.A.Const. art. 1, § 8.

[11] **Patents ⚷16(1)**
291k16(1) Most Cited Cases
(Formerly 291k16)
It is duty of commissioner of patents and of courts in administration of patent system to give effect to constitutional standard by appropriate application in each case of statutory scheme.

[12] **Patents ⚷16.10(2)**
291k16.10(2) Most Cited Cases
(Formerly 291k16.11)
Clause of Patent Act pertaining to nonpatentability of invention because of obviousness declaring "patentability shall not be negatived by the manner in which the invention was made" eliminated any requirement for a "flash of genius". 35 U.S.C.A. § 103.

[13] **Patents ⚷16(1)**
291k16(1) Most Cited Cases
(Formerly 291k16, 291k18)
Emphasis on nonobviousness in determining patentability is one of inquiry, not quality, and as such comports with constitutional strictures. 35 U.S.C.A. § 103; U.S.C.A.Const. art. 1, § 8.

[14] **Patents ⚷16.13**
291k16.13 Most Cited Cases
Ultimate question of patent validity is one of law.

[15] **Patents ⚷16(2)**
291k16(2) Most Cited Cases
(Formerly 291k18)
Under Patent Act provision pertaining to nonobviousness as condition for patentability, scope and content of prior art are to be determined, differences between prior art and claims at issue are to be ascertained, and level of ordinary skill in pertinent art resolved; and against this background obviousness or nonobviousness of subject matter is determined. 35 U.S.C.A. § 103.

[16] **Patents ⚷36.1(1)**
291k36.1(1) Most Cited Cases
(Formerly 291k18)

[16] **Patents ⚷36.1(3)**
291k36.1(3) Most Cited Cases
(Formerly 291k16.7)

[16] **Patents ⚷36.2(1)**
291k36.2(1) Most Cited Cases
(Formerly 291k36(2))
Such secondary considerations as commercial success, long-felt but unsolved
needs, and failure of others, might be utilized to give light to circumstances surrounding origin of subject matter sought to be patented as indicia of obviousness or nonobviousness. 35 U.S.C.A. § 103.

[17] **Patents ⚷328(2)**
291k328(2) Most Cited Cases
(Formerly 291k328)
2,627,798. Patent No. 2,627,798, relating to spring clamp which permitted plow shanks to be pushed up-

ward when they struck obstructions in soil and to spring back into normal position when obstruction was passed over, was invalid because of obviousness of subject matter. 35 U.S.C.A. § 103.

[18] **Patents ⇐168(1)**
291k168(1) Most Cited Cases
Invention is construed not only in light of claims but also with reference to file wrapper or prosecution history in patent office.

[19] **Patents ⇐168(2.2)**
291k168(2.2) Most Cited Cases
Cancellation.
(Formerly 291k168(21/4))
Claims as allowed must be read and interpreted with reference to rejected ones and to state of prior art, and claims that have been narrowed in order to obtain issuance of patent by distinguishing prior art cannot be sustained to cover that which was previously by limitation eliminated from patent.

[20] **Patents ⇐168(2.2)**
291k168(2.2) Most Cited Cases
(Formerly 291k168(21/4))
Where patentee obtained patent only by accepting limitations imposed by patent examiner and claims were carefully drafted to reflect such limitations, broader view of invention could not thereafter be asserted.

[21] **Patents ⇐328(2)**
291k328(2) Most Cited Cases
(Formerly 291k328)
2,870,943. Patent No. 2,870,943, relating to plastic finger sprayer with "hold down" lid used as built-in dispenser for containers or bottles packaging liquid products, principally household insecticides, was invalid because of obviousness of subject matter. 35 U.S.C.A. § 103.

Patents ⇐328(4)
291k328(4) Most Cited Cases
1,447,712, 2,844,290, 2,118,222, 2,119,884, 2,493,811, 2,586,687, 2,751,480. Cited.
****686 *2** No. 11:

Orville O. Gold, Kansas City, Mo., for petitioners.

S. Tom Morris, Amarillo, Tex., for respondents.

Nos. 37, 43:

Dennis G. Lyons, Washington, D.C., for petitioners.

Gordon D. Schmidt, Kansas City, Mo., for respondent.

***3** Mr. Justice CLARK delivered the opinion of the Court.

After a lapse of 15 years, the Court again focuses its attention on the patentability of inventions under the standard of Art. I, s 8, cl. 8, of the Constitution and under the conditions prescribed by the laws of the United States. Since our last expression on patent validity, Great A. & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 71 S.Ct. 127, 95 L.Ed. 162 (1950), the Congress has for the first time expressly added a third statutory dimension to the two requirements of novelty and utility that had been the sole statutory test since the Patent Act of 1793. This is the test of obviousness, i.e., whether 'the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.' s 103 of the Patent Act of 1952, 35 U.S.C. s 103 (1964 ed.).

[1] The questions, involved in each of the companion cases before us, are what effect the 1952 Act had upon traditional statutory and judicial tests of patentability and what definitive tests are now required. We have concluded that the 1952 Act was intended to codify judicial precedents embracing the principle long ago ***4** announced by this Court in Hotchkiss v. Greenwood, 11 How. 248, 13 L.Ed. 683 (1851), and that, while the clear language of s 103 places emphasis on an inquiry into obviousness, the general ****687** level of innovation necessary to sustain patentability remains the same.

I.

The Cases.

(a). No. 11, Graham v. John Deere Co., an infringement suit by petitioners, presents a conflict between two Circuits over the validity of a single patent on a 'Clamp for vibrating Shank Plows.' The invention, a combination of old mechanical elements, involves a device designed to absorb shock from plow shanks as they plow through rocky soil and thus to prevent damage to the plow. In 1955, the Fifth Circuit had held the patent valid under its rule that when a combination produces an 'old result in a cheaper and otherwise more advantageous way,' it is patentable. Jeoffroy Mfg., Inc. v. Graham, 219 F.2d 511, cert. denied, 350 U.S. 826, 76 S.Ct. 55, 100 L.Ed. 738. In 1964, the Eighth Circuit held, in the case at bar, that there was no new result in the patented combination and that the patent was, therefore, not valid. 333 F.2d 529, reversing D.C., 216 F.Supp. 272. We granted certiorari, 379 U.S. 956, 85 S.Ct. 652, 13 L.Ed.2d 553. Although we have determined that neither Circuit applied the correct test, we conclude that the patent is invalid under s 103 and, therefore, we affirm the judgment of the Eighth Circuit.

(b). No. 37, Calmar, Inc. v. Cook Chemical Co., and No. 43, Colgate-Palmolive Co. v. Cook Chemical Co., both from the Eighth Circuit, were separate declaratory judgment actions, but were filed contemporaneously. Petitioner in Calmar is the manufacturer of a finger-operated sprayer with a 'hold-down' cap of the type commonly seen on grocers' shelves inserted in bottles of insecticides and other liquids prior to shipment. Petitioner in Colgate-Palmolive is a purchaser of the sprayers and *5 uses them in the distribution of its products. Each action sought a declaration of invalidity and noninfringement of a patent on similar sprayers issued to Cook Chemical as assignee of Baxter I. Scoggin, Jr., the inventor. By cross-action, Cook Chemical claimed infringement. The actions were consolidated for trial and the patent was sustained by the District Court. 220 F.Supp. 414. The Court of Appeals affirmed, 8 Cir., 336 F.2d 110, and we granted certiorari, 380 U.S. 949, 85 S.Ct. 1082, 13 L.Ed.2d 967. We reverse.

Manifestly, the validity of each of these patents turns on the facts. The basic problems, however, are the same in each case and require initially a discussion of the constitutional and statutory provisions covering the patentability of the inventions.

II.

[2][3][4][5][6][7] At the outset it must be remembered that the federal patent power stems from a specific constitutional provision which authorizes the Congress 'To promote the Progress of * * * useful Arts, by securing for limited Times to * * * Inventors the exclusive Right to their * * * Discoveries.' Art. I, s 8, cl. 8. [FN1] The clause is both a grant of power and a limitation. This qualified authority, unlike the power often exercised in the sixteenth and seventeenth centuries by the English Crown, is limited to the promotion of advances in the 'useful arts.' It was written against the backdrop of the practices--eventually curtailed by the Statute of Monopolies--of the Crown in granting monopolies to court favorites in goods or businesses which had long before been enjoyed by the public. See Meinhardt, Inventions, Patents and Monopoly, pp. **688 30--35 (London, 1946). The Congress in the *6 exercise of the patent power may not overreach the restraints imposed by the stated constitutional purpose. Nor may it enlarge the patent monopoly without regard to the innovation, advancement or social benefit gained thereby. Moreover, Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must 'promote the Progress of * * * useful Arts.' This is the standard expressed in the Constitution and it may not be ignored. And it is in this light that patent validity 'requires reference to a standard written into the Constitution.' Great A. & P. Tea Co. v. Supermarket Equipment Corp., supra, 340 U.S. at 154, 71 S.Ct. at 131 (concurring opinion).

> FN1. The provision appears in the Constitution spliced together with the copyright provision, which we omit as not relevant here. See H.R.Rep.No.1923, 82d Cong., 2d Sess., at 4 (1952); DeWolf, An Outline of Copyright Law, p. 15 (Boston, 1925).

[8][9][10][11] Within the limits of the constitutional

grant, the Congress may, of course, implement the stated purpose of the Framers by selecting the policy which in its judgment best effectuates the constitutional aim. This is but a corollary to the grant to Congress of any Article I power. Gibbons v. Ogden, 9 Wheat. 1, 6 L.Ed. 23. Within the scope established by the Constitution, Congress may set out conditions and tests for patentability. McClurg v. Kingsland, 1 How. 202, 206, 11 L.Ed. 102. It is the duty of the Commissioner of Patents and of the courts in the administration of the patent system to give effect to the constitutional standard by appropriate application, in each case, of the statutory scheme of the Congress.

Congress quickly responded to the bidding of the Constitution by enacting the Patent Act of 1790 during the second session of the First Congress. It created an agency in the Department of State headed by the Secretary of State, the Secretary of the Department of War *7 and the Attorney General, any two of whom could issue a patent for a period not exceeding 14 years to any petitioner that 'hath * * * invented or discovered any useful art, manufacture, * * * or device, or any improvement therein not before known or used' if the board found that 'the invention or discovery (was) sufficiently useful and important * * *.' 1 Stat. 110. This group, whose members administered the patent system along with their other public duties, was known by its own designation as 'Commissioners for the Promotion of Useful Arts.'

Thomas Jefferson, who as Secretary of State was a member of the group, was its moving spirit and might well be called the 'first administrator of our patent system.' See Federico, Operation of the Patent Act of 1790, 18 J.Pat.Off.Soc. 237, 238 (1936). He was not only an administrator of the patent system under the 1790 Act, but was also the author of the 1793 Patent Act. In addition, Jefferson was himself an inventor of great note. His unpatented improvements on plows, to mention but one line of his inventions, won acclaim and recognition on both sides of the Atlantic. Because of his active interest and influence in the early development of the patent system, Jefferson's views on the general nature of the limited patent monopoly under the Constitution, as well as his conclusions as to conditions for patentability under the statutory scheme, are worthy of note.

Jefferson, like other Americans, had an instinctive aversion to monopolies. It was a monopoly on tea that sparked the Revolution and Jefferson certainly did not favor an equivalent form of monopoly under the new government. His abhorrence of monopoly extended initially to patents as well. From France, he wrote to Madison (July 1788) urging a Bill of Rights provision restricting monopoly, and as against the argument that *8 limited **689 monopoly might serve to incite 'ingenuity,' he argued forcefully that 'the benefit even of limited monopolies is too doubtful to be opposed to that of their general suppression,' V Writings of Thomas Jefferson, at 47 (Ford ed., 1895).

His views ripened, however, and in another letter to Madison (Aug. 1789) after the drafting of the Bill of Rights, Jefferson stated that he would have been pleased by an express provision in this form:

> 'Art. 9. Monopolies may be allowed to persons for their own productions in literature, & their own inventions in the arts, for a term not exceeding _ _ years, but for no longer term & no other purpose.' Id., at 113.

And he later wrote:

> 'Certainly an inventor ought to be allowed a right to the benefit of his invention for some certain time. * * * Nobody wishes more than I do that ingenuity should receive a liberal encouragement.' Letter to Oliver Evans (May 1807), V Writings of Thomas Jefferson, at 75--76 (Washington ed.).

Jefferson's philosophy on the nature and purpose of the patent monopoly is expressed in a letter to Isaac McPherson (Aug. 1813), a portion of which we set out in the margin. [FN2] He rejected a natural-rights theory in *9 intellectual property rights and clearly recognized the social and economic rationale of the patent system. The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge. The grant of an exclusive right to an invention was the creation of society--at odds with the inherent free nature of disclosed ideas--and was not to be freely given. Only inventions and discoveries which furthered human knowledge, and were new and useful, justified the special inducement of a limited private monopoly. Jefferson did not believe in granting patents for small details,

obvious improvements, or frivolous devices. His writings evidence his insistence upon a high level of patentability.

> FN2. 'Stable ownership is the gift of social law, and is given late in the progress of society. It would be curious then, if an idea, the fugitive fermentation of an individual brain, could, of natural right, be claimed in exclusive and stable property. If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it. He who receives an idea from me, receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening me. That ideas should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature, when she made them, like fire, expansible over all space, without lessening their density in any point, and like the air in which we breathe, move, and have our physical being, incapable of confinement or exclusive appropriation. Inventions then cannot, in nature, be a subject of property. Society may give an exclusive right to the profits arising from them, as an encouragement to men to pursue ideas which may produce utility, but this may or may not be done, according to the will and convenience of the society, without claim or complaint from anybody.' VI Writings of Thomas Jefferson, at 180--181 (Washington ed.).

As a member of the patent board for several years, Jefferson saw clearly the difficulty in 'drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not.' The board on which he served sought to draw such a line and formulated several rules which ****690** are preserved in ***10** Jefferson's correspondence. [FN3] Despite the board's efforts, Jefferson saw 'with what slow progress a system of general rules could be matured.' Because of the 'abundance' of cases and the fact that the investigations occupied 'more time of the members of the board than they could spare from higher duties, the whole was turned over to the judiciary, to be matured into a system, under which every one might know when his actions were safe and lawful.' Letter to McPherson, supra, at 181, 182. Apparently Congress agreed with Jefferson and the board that the courts should develop additional conditions for patentability. Although the Patent Act was amended, revised or codified some 50 times between 1790 and 1950, Congress steered clear of a statutory set of requirements other than the bare novelty and utility tests reformulated in Jefferson's draft of the 1793 Patent Act.

> FN3. '(A) machine of which we are possessed, might be applied by every man to any use of which it is susceptible.' Letter to Isaac McPherson, supra, at 181.
> '(A) change of material should not give title to a patent. As the making a ploughshare of cast rather than of wrought iron; a comb of iron instead of horn or of ivory * * *.' Ibid.
> '(A) mere change of form should give no right to a patent, as a high-quartered shoe instead of a low one; a round hat instead of a three-square; or a square bucket instead of a round one.' Id., at 181--182.
> '(A combined use of old implements.) A man has a right to use a saw, an axe, a plane separately; may he not combine their uses on the same piece of wood?' Letter to Oliver Evans, (Jan. 1814), VI Writings of Thomas Jefferson, at 298 (Washington ed.).

III.

The difficulty of formulating conditions for patentability was heightened by the generality of the constitutional grant and the statutes implementing it, together with the underlying policy of the patent system that 'the things which are worth to the public the embar-

rassment *11 of an exclusive patent,' as Jefferson put it, must outweigh the restrictive effect of the limited patent monopoly. The inherent problem was to develop some means of weeding out those inventions which would not be disclosed or devised but for the inducement of a patent.

This Court formulated a general condition of patentability in 1851 in Hotchkiss v. Greenwood, 11 How. 248, 13 L.Ed. 683. The patent involved a mere substitution of materials--porcelain or clay for wood or metal in doorknobs--and the Court condemned it, holding: [FN4]

> FN4. In historical retrospect, the specific result in Hotchkiss flows directly from an application of one of the rules of the original board of 'Commissioners,' n. 3, second rule, supra.

> '(U)nless more ingenuity and skill * * * were required * * * than were possessed by an ordinary mechanic acquainted with the business, there was an absence of that degree of skill and ingenuity which constitute essential elements of every invention. In other words, the improvement is the work of the skilful mechanic, not that of the inventor.' At p. 267.

Hotchkiss, by positing the condition that a patentable invention evidence more ingenuity and skill than that possessed by an ordinary mechanic acquainted with the business, merely distinguished between new and useful innovations that were capable of sustaining a patent and those that were not. The Hotchkiss test laid the cornerstone of the judicial evolution suggested by Jefferson and left to the courts by Congress. The language in the case, and in those which followed, gave birth to 'invention' as a word of legal art signifying patentable inventions. Yet, as this Court has observed, '(t)he truth is, the word ('invention') cannot be defined in such manner as **691 to afford any substantial aid in determining whether a particular device involves an exercise of the inventive faculty *12 or not.' McClain v. Ortmayer, 141 U.S. 419, 427, 12 S.Ct. 76, 78, 35 L.Ed. 800 (1891); Great A. & P. Tea Co. v. Supermarket Equipment Corp., supra, 340 U.S., at 151, 71 S.Ct. at 129. Its use as a label brought about a large variety of opinions as to its meaning both in the Patent Office, in the courts, and at the bar. The Hotchkiss formulation, however, lies not in any label, but in its functional approach to questions of patentability. In practice, Hotchkiss has required a comparison between the subject matter of the patent, or patent application, and the background skill of the calling. It has been from this comparison that patentability was in each case determined.

IV.

The 1952 Patent Act.

The Act sets out the conditions of patentability in three sections. An analysis of the structure of these three sections indicates that patentability is dependent upon three explicit conditions: novelty and utility as articulated and defined in s 101 and s 102, and nonobviousness, the new statutory formulation, as set out in s 103. The first two sections, which trace closely the 1874 codification, express the 'new and useful' tests which have always existed in the statutory scheme and, for our purposes here, need no clarification. [FN5] The pivotal *13 section around which the present controversy centers is s 103. It provides:

> FN5. 's 101. Inventions patentable
> 'Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.'
> 's 102. Conditions for patentability; novelty and loss of right to patent
> 'A person shall be entitled to a patent unless--
> '(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
> '(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

'(c) he has abandoned the invention, or
'(d) the invention was first patented or caused to be patented by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application filed more than twelve months before the filing of the application in the United States, or
'(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or
'(f) he did not himself invent the subject matter sought to be patented, or
'(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.'
The precursors of these sections are to be found in the Act of February 21, 1793, c. 11, 1 Stat. 318; Act of July 4, 1836, c. 357, 5 Stat. 117; Act of July 8, 1870, c. 230, 16 Stat. 198; Rev.Stat. s 4886 (1874).

's 103. Conditions for patentability; non-obvious subject matter
'A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention ****692** was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.'

***14** The section is cast in relatively unambiguous terms. Patentability is to depend, in addition to novelty and utility, upon the 'non-obvious' nature of the 'subject matter sought to be patented' to a person having ordinary skill in the pertinent art.

The first sentence of this section is strongly reminiscent of the language in Hotchkiss. Both formulations place emphasis on the pertinent art existing at the time the invention was made and both are implicitly tied to advances in that art. The major distinction is that Congress has emphasized 'nonobviousness' as the operative test of the section, rather than the less definite 'invention' language of Hotchkiss that Congress thought had led to 'a large variety' of expressions in decisions and writings. In the title itself the Congress used the phrase 'Conditions for patentability; non-obvious subject matter' (italics added), thus focusing upon 'nonobviousness' rather than 'invention.' [FN6] The Senate and House Reports, S.Rep. No. 1979, 82d Cong., 2d Sess. (1952); H.R.Rep. No. 1923, 82d Cong., 2d Sess. (1952), U.S.Code Congressional and Administrative News 1952, p. 2394, reflect this emphasis in these terms:

FN6. The corresponding provision in the preliminary draft was titled 'Conditions for patentability, lack of invention' (italics added), Proposed Revision and Amendment of the Patent Laws, Preliminary Draft with Notes, House Committee on the Judiciary (Committee Print, 1950).

'Section 103, for the first time in our statute, provides a condition which exists in the law and has existed for more than 100 years, but only by reason of decisions of the courts. An invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent. That has been expressed in a large variety of ways in decisions of ***15** the courts and in writings. Section 103 states this requirement in the title. It refers to the difference between the subject matter sought to be patented and the prior art, meaning what was known before as described in section 102. If this difference is such that the subject matter as a whole would have been obvious at the time to a person skilled in the art, then the subject matter

cannot be patented.

'That provision paraphrases language which has often been used in decisions of the courts, and the section is added to the statute for uniformity and definiteness. This section should have a stabilizing effect and minimize great departures which have appeared in some cases.' H.R.Rep., supra, at 7; S.Rep., supra, at 6.

[12] It is undisputed that this section was, for the first time, a statutory expression of an additional requirement for patentability, originally expressed in Hotchkiss. It also seems apparent that Congress intended by the last sentence of s 103 to abolish the test it believed this Court announced in the controversial phrase 'flash of creative genius,' used in Cuno Engineering Corp. v. Automatic Devices Corp., 314 U.S. 84, 62 S.Ct. 37, 86 L.Ed. 58 (1941). [FN7]

FN7. The sentence in which the phrase occurs reads: '(T)he new device, however useful it may be, must reveal the flash of creative genius not merely the skill of the calling.' At p. 91, 62 S.Ct. at p. 41. Although some writers and lower courts found in the language connotations as to the frame of mind of the inventors, none Hotchkiss specifically, and the reference to 'flash of creative genius' was but a rhetorical embellishment of language going back to 1833. Cf. 'exercise of genius,' Shaw v. Cooper, 7 Pet. 292, 8 L.Ed. 689; 'inventive genius,' Reckendorfer v. Faber, 92 U.S. 347, 23 L.Ed. 719 (1876); Concrete Appliance Co. v. Gomery, 269 U.S. 177, 46 S.Ct. 42, 70 L.Ed. 222; 'flash of thought,' Densmore v. Scofield, 102 U.S. 375, 26 L.Ed. 214 (1880); 'intuitive genius,' Potts v. Creager, 155 U.S. 597, 15 S.Ct. 194, 39 L.Ed. 275 (1895). Rather than establishing a more exacting standard, Cuno merely rhetorically restated the requirement that the subject matter sought to be patented must be beyond the skill of the calling. It was the device, not the invention, that had to reveal the 'flash of creative genius.' See Boyajian, The Flash of Creative Genius, An Alternative Interpretation, 25 J.Pat.Off.Soc. 776, 780, 781 (1943); Pacific Contact Laboratories, Inc. v. Solex Laboratories, Inc., 9 Cir., 209 F.2d 529, 533; Brown & Sharpe Mfg. Co. v. Kar Engineering Co., 1 Cir., 154 F.2d 48, 51--52; In re Shortell, 142 F.2d 292, 295--296, 31 CCPA (Pat.) 1062, 1069.

****693 *16** It is contended, however, by some of the parties and by several of the amici that the first sentence of s 103 was intended to sweep away judicial precedents and to lower the level of patentability. Others contend that the Congress intended to codify the essential purpose reflected in existing judicial precedents--the rejection of insignificant variations and innovations of a commonplace sort--and also to focus inquiries under s 103 upon nonobviousness, rather than upon 'invention,' as a means of achieving more stability and predictability in determining patentability and validity.

The Reviser's Note to this section, [FN8] with apparent reference to Hotchkiss, recognizes that judicial requirements as to 'lack of patentable novelty (have) been followed since at least as early as 1850.' The note indicates that the section was inserted because it 'may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.' To this same effect are the reports of both Houses, supra, which state that the first sentence ***17** of the section 'paraphrases language which has often been used in decisions of the courts, and the section is added to the statute for uniformity and definiteness.'

FN8. 'There is no provision corresponding to the first sentence explicitly stated in the present statutes, but the refusal of patents by the Patent Office, and the holding of patents invalid by the courts, on the ground of lack of invention or lack of patentable novelty has been followed since at least as early as 1850. This paragraph is added with the view that an explicit statement in the statute may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.

'The second sentence states that patentability

> as to this requirement is not to be negatived by the manner in which the invention was made, that is, it is immaterial whether it resulted from long toil and experimentation or from a flash of genius.'

We believe that this legislative history, as well as other sources, [FN9] shows that the revision was not intended by Congress to change the general level of patentable invention. We conclude that the section was intended merely as a codification of judicial precedents embracing the Hotchkiss condition, with congressional directions that inquiries into the obviousness of the subject matter sought to be patented are a prerequisite to patentability.

> FN9. See Efforts to Establish a Statutory Standard of Invention, Study No. 7, Senate Subcommittee on Patents, Trademarks, and Copyrights, 85th Cong., 1st Sess. (Committee Print, 1958); Hearings, Subcommittee No. 3, House Committee on the Judiciary, on H.R. 3760, 82d Cong., 1st Sess. (1951).

V.

[13] Approached in this light, the s 103 additional condition, when followed realistically, will permit a more practical test of patentability. The emphasis on non-obviousness is one of inquiry, not ****694** quality, and, as such, comports with the constitutional strictures.

[14][15][16] While the ultimate question of patent validity is one of law, Great A. & P. Tea Co. v. Supermarket Equipment Corp., supra, 340 U.S. at 155, 71 S.Ct. at 131, the s 103 condition, which is but one of three conditions, each of which must be satisfied, lends itself to several basic factual inquiries. Under s 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances ***18** surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy. See Note, Subtests of 'Nonobviousness': A Nontechnical Approach to Patent Validity, 112 U.Pa.L.Rev. 1169 (1964).

This is not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definiteness which Congress called for in the 1952 Act.

While we have focused attention on the appropriate standard to be applied by the courts, it must be remembered that the primary responsibility for sifting out unpatentable material lies in the Patent Office. To await litigation is-- for all practical purposes--to debilitate the patent system. We have observed a notorious difference between the standards applied by the Patent Office and by the courts. While many reasons can be adduced to explain the discrepancy, one may well be the free rein often exercised by Examiners in their use of the concept of 'invention.' In this connection we note that the Patent Office is confronted with a most difficult task. Almost 100,000 applications for patents are filed each year. Of these, about 50,000 are granted and the backlog now runs well over 200,000. 1965 Annual Report of the Commission of Patents 13--14. This is itself a compelling reason for the Commissioner to strictly adhere to the 1952 Act as interpreted here. This would, we believe, not only expedite disposition but ***19** bring about a closer concurrence between administrative and judicial precedent. [FN10]

> FN10. The President has appointed a Commission on the Patent System, Executive Order No. 11215, 30 Fed.Reg. 4661 (April 10, 1965). It is hoped that its studies may develop more efficient administrative procedures and techniques that will further expedite dis-

positions and at the same time insure the strict application of appropriate tests of patentability.

Although we conclude here that the inquiry which the Patent Office and the courts must make as to patentability must be beamed with greater intensity on the requirements of s 103, it bears repeating that we find no change in the general strictness with which the overall test is to be applied. We have been urged to find in s 103 a relaxed standard, supposedly a congressional reaction to the 'increased standard' applied by this Court in its decisions over the last 20 or 30 years. The standard has remained invariable in this Court. Technology, however, has advanced--and with remarkable rapidity in the last 50 years. Moreover, the ambit of applicable art in given fields of science has widened by ****695** disciplines unheard of a half century ago. It is but an evenhanded application to require that those persons granted the benefit of a patent monopoly be charged with an awareness of these changed conditions. The same is true of the less technical, but still useful arts. He who seeks to build a better mousetrap today has a long path to tread before reaching the Patent Office.

VI.

We now turn to the application of the conditions found necessary for patentability to the cases involved here:

A. The Patent in Issue in No. 11, Graham v. John Deere Co.

This patent, No. 2,627,798 (hereinafter called the '798 patent) relates to a spring clamp which permits plow shanks to be pushed upward when they hit obstructions ***20** in the soil, and then springs the shanks back into normal position when the obstruction is passed over. The device, which we show diagrammatically in the accompanying sketches (Appendix, Fig. 1), is fixed to the plow frame as a unit. The mechanism around which the controversy center is basically a hinge. The top half of it, known as the upper plate (marked 1 in the sketches), is a heavy metal piece clamped to the plow frame (2) and is stationary relative to the plow frame. The lower half of the hinge, known as the hinge plate (3), is connected to the rear of the upper plate by a hinge pin (4) and rotates downward with respect to it. The shank (5), which is bolted to the forward end of the hinge plate (at 6), runs beneath the plate and parallel to it for about nine inches, passes through a stirrup (7), and then continues backward for several feet curving down toward the ground. The chisel (8), which does the actual plowing, is attached to the rear end of the shank. As the plow frame is pulled forward, the chisel rips through the soil, thereby plowing it. In the normal position, the hinge plate and the shank are kept tight against the upper plate by a spring (9), which is atop the upper plate. A rod (10) runs through the center of the spring, extending down through holes in both plates and the shank. Its upper end is bolted to the top of the spring while its lower end is hooked against the underside of the shank.

When the chisel hits a rock or other obstruction in the soil, the obstruction forces the chisel and the rear portion of the shank to move upward. The shank is pivoted (at 11) against the rear of the hinge plate and pries open the hinge against the closing tendency of the spring. (See sketch labeled 'Open Position,' Appendix, Fig. 1.) This closing tendency is caused by the fact that, as the hinge is opened, the connecting rod is pulled downward and the spring is compressed. When the obstruction ***21** is passed over, the upward force on the chisel disappears and the spring pulls the shank and hinge plate back into their original position. The lower, rear portion of the hinge plate is constructed in the form of a stirrup (7) which brackets the shank, passing around and beneath it. The shank fits loosely into the stirrup (permitting a slight up and down play). The stirrup is designed to prevent the shank from recoiling away from the hinge plate, and thus prevents excessive strain on the shank near its bolted connection. The stirrup also girds the shank, preventing it from fishtailing from side to side.

In practical use, a number of spring-hinge-shank combinations are clamped to a plow frame, forming a set of ground-working chisels capable of withstanding the shock of rocks and other obstructions in the soil without breaking the shanks.

Background of the Patent.

Chisel plows, as they are called, were developed for plowing in areas where the ground is relatively free from rocks or ****696** stones. Originally, the shanks were rigidly attached to the plow frames. When such plows were used in the rocky, glacial soils of some of the Northern States, they were found to have serious defects. As the chisels hit buried rocks, a vibratory motion was set up and tremendous forces were transmitted to the shank near its connection to the frame. The shanks would break. Graham, one of the petitioners, sought to meet that problem, and in 1950 obtained a patent, U.S. No. 2,493,811 (hereinafter '811), on a spring clamp where solved some of the difficulties. Graham and his companies manufactured and sold the '811 clamps. In 1950, Graham modified the '811 structure and filed for a patent. That patent, the one in issue, was granted in 1953. This suit against competing plow manufacturers resulted from charges by petitioners that several of respondents' devices infringed the '798 patent.

***22** The Prior Art.

Five prior patents indicating the state of the art were cited by the Patent Office in the prosecution of the '798 application. Four of these patents, 10 other United States patents and two prior-use spring-clamp arrangements not of record in the '798 file wrapper were relied upon by respondents as revealing the prior art. The District Court and the Court of Appeals found that the prior art 'as a whole in one form or another contains all of the mechanical elements of the 798 Patent.' One of the prior-use clamp devices not before the Patent Examiner--Glencoe--was found to have 'all of the elements.'

We confine our discussion to the prior patent of Graham, '811, and to the Glencoe clamp device, both among the references asserted by respondents. The Graham '811 and '798 patent devices are similar in all elements, save two: (1) the stirrup and the bolted connection of the shank to the hinge plate do not appear in '811; and (2) the position of the shank is reversed, being placed in patent '811 above the hinge plate, sandwiched between it and the upper plate. The shank is held in place by the spring rod which is hooked against the bottom of the hinge plate passing through a slot in the shank. Other differences are of no consequence to our examination. In practice the '811 patent arrangement permitted the shank to wobble or fishtail because it was not rigidly fixed to the hinge plate; moreover, as the hinge plate was below the shank, the latter caused wear on the upper plate, a member difficult to repair or replace.

Graham's '798 patent application contained 12 claims. All were rejected as not distinguished from the Graham '811 patent. The inverted position of the shank was specifically rejected as was the bolting of the shank to the hinge plate. The Patent Office examiner found these to be 'matters of design well within the expected skill of ***23** the art and devoid of invention.' Graham withdrew the original claims and substituted the two new ones which are substantially those in issue here. His contention was that wear was reduced in patent '798 between the shank and the heel or rear of the upper plate. [FN11] He also emphasized several new features, the relevant one here being that the bolt used to connect the hinge plate and shank maintained the upper face of the shank in continuing ****697** and constant contact with the underface of the hinge plate.

> FN11. In '811, where the shank was above the hinge plate, an upward movement of the chisel forced the shank up against the underside of the rear of the upper plate. The upper plate thus provided the fulcrum about which the hinge was pried open. Because of this, as well as the location of the hinge pin, the shank rubbed against the heel of the upper plate causing wear both to the plate and to the shank. By relocating the hinge pin and by placing the hinge plate between the shank and the upper plate, as in '798, the rubbing was eliminated and he wear point was changed to the hinge plate, a member more easily removed or replaced for repair.

Graham did not urge before the Patent Office the greater 'flexing' qualities of the '798 patent arrangement which he so heavily relied on in the courts. The sole element in patent '798 which petitioners argue before us is the interchanging of the shank and hinge plate and the consequences flowing from this arrangement. The contention is that this arrangement-

-which petitioners claim is not disclosed in the prior art--permits the shank to flex under stress for its entire length. As we have sketched (see sketch, 'Graham '798 Patent' in Appendix, Fig. 2), when the chisel hits an obstruction the resultant force (A) pushes the rear of the shank upward and the shank pivots against the rear of the hinge plate at (C). The natural tendency is for that portion of the shank between the pivot point and the bolted connection (i.e., between C and D) to bow downward and away from the hinge plate. The maximum distance (***24** B) that the shank moves away from the plate is slight--for emphasis, greatly exaggerated in the sketches. This is so because of the strength of the shank and the short--nine inches or so--length of that portion of the shank between (C) and (D). On the contrary, in patent '811 (see sketch, 'Graham '811 Patent' in Appendix, Fig. 2), the pivot point is the upper plate at point (c); and while the tendency for the shank to bow between points (c) and (d) is the same as in '798, the shank is restricted because of the underlying hinge plate and cannot flex as freely. In practical effect, the shank flexes only between points (a) and (c), and not along the entire length of the shank, as in '798. Petitioners say that this difference in flex, though small, effectively absorbs the tremendous forces of the shock of obstructions whereas prior art arrangements failed.

The Obviousness of the Differences.

[17] We cannot agree with petitioners. We assume that the prior art does not disclose such an arrangement as petitioners claim in patent '798. Still we do not believe that the argument on which petitioners' contention is bottomed supports the validity of the patent. The tendency of the shank to flex is the same in all cases. If free-flexing, as petitioners now argue, is the crucial difference above the prior art, then it appears evident that the desired result would be obtainable by not boxing the shank within the confines of the hinge. [FN12] The only other effective place available in the arrangement was to attach it below the hinge plate and run it through a ***25** stirrup or bracket that would not disturb its flexing qualities. Certainly a person having ordinary skill in the prior art, given the fact that the flex in the shank could be utilized more effectively if allowed to run the entire length of the shank, would immediately see that the thing to do was what Graham did, i.e., invert the shank and the hinge plate.

> FN12. Even petitioners' expert testified to that effect:
> 'Q. Given the same length of the forward portion of the clamp * * * you would anticipate that the magnitude of flex (in '798) would be precisely the same or substantially the same as in 811, wouldn't you?
> 'A. I would think so.'

Petitioners' argument basing validity on the free-flex theory raised for the first time on appeal is reminiscent of Lincoln Engineering Co. of Illinois v. Stewart-Warner Corp., 303 U.S. 545, 58 S.Ct. 662, 82 L.Ed. 1008 (1938), where the Court called such an effort 'an afterthought. No such function * * * is hinted at in the specifications of the patent. If this were so vital an element in the functioning of the apparatus, it is strange that all mention of it was omitted.' At p. 550, 58 S.Ct. at p. 665. No 'flexing' argument ****698** was raised in the Patent Office. Indeed, the trial judge specifically found that 'flexing is not a claim of the patent in suit * * *' and would not permit interrogation as to flexing in the accused devices. Moreover, the clear testimony of petitioners' experts shows that the flexing advantages flowing from the '798 arrangement are not, in fact, a significant feature in the patent. [FN13]

> FN13. 'Q. * * * Do you regard the small degree of flex in the forward end of the shank that lies between the pivot point and the point of spring attachment to be of any significance or any importance to the functioning of a device such as 798? A. Unless you are approaching the elastic limit, I think this flexing will reduce the maximum stress at the point of pivot there, where the maximum stress does occur. I think it will reduce that. I don't know how much.
> 'Q. Do you think it is a substantial factor, a factor of importance in the functioning of the structure? A. Not a great factor, no.'
> The same expert previously testified similarly in Jeoffoy Mfg., Inc. v. Graham, 219 F.2d 511.

We find no nonobvious facets in the '798 arrangement. The wear and repair claims were sufficient to overcome ***26** the patent examiner's original conclusions as to the validity of the patent. However, some of the prior art, notably Glencoe, was not before him. There the hinge plate is below the shank but, as the courts below found, all of the elements in the '798 patent are present in the Glencoe structure. Furthermore, even though the position of the shank and hinge plate appears reversed in Glencoe, the mechanical operation is identical. The shank there pivots about the underside of the stirrup, which in Glencoe is above the shank. In other words, the stirrup in Glencoe serves exactly the same function as the heel of the hinge plate in '798. The mere shifting of the wear point to the heel of the '798 hinge plate from the stirrup of Glencoe--itself a part of the hinge plate--presents no operative mechanical distinctions, much less nonobvious differences.

B. The Patent in Issue in No. 37, Calmar, Inc. v. Cook Chemical Co., and in No. 43, Colgate-Palmolive Co. v. Cook Chemical Co.

The single patent [FN14] involved in these cases relates to a plastic finger sprayer with a 'hold-down' lid used as a built-in dispenser for containers or bottles packaging liquid products, principally household insecticides. Only the first two of the four claims in the patent are involved here and we, therefore, limit our discussion to them. We do not set out those claims here since they are printed in 220 F.Supp., at 417--418.

> FN14. The patent is U.S. No. 2,870,943 issued in 1959 to Cook Chemical Co. as assignee of Baxter I. Scoggin, Jr., the inventor. In No. 37, Calmar is the manufacturer of an alleged infringing device, and, in No. 43, Colgate is a customer of Calmar and user of its device.

In essence the device here combines a finger-operated pump sprayer, mounted in a container or bottle by means of a container cap, with a plastic overcap which screws over the top of and depresses the sprayer (see Appendix, ***27** Fig. 3). The pump sprayer passes through the container cap and extends down into the liquid in the container; the overcap fits over the pump sprayer and screws down on the outside of a collar mounting or retainer which is molded around the body of the sprayer. When the overcap is screwed down on this collar mounting a seal is formed by the engagement of a circular ridge or rib located above the threads on the collar mounting with a mating shoulder located inside the overcap above its threads. [FN15] The overcap, as it is screwed down, depresses the pump plunger rendering the pump inoperable and when the seal is effected, ****699** any liquid which might seep into the overcap through or around the pump is prevented from leaking out of the overcap. The overcap serves also to protect the sprayer head and prevent damage to it during shipment or merchandising. When the overcap is in place it does not reach the cap of the container or bottle and in no way engages it since a slight space is left between those two pieces.

> FN15. Our discussion here relates to the overcap seal. The container itself is sealed in the customary way through the use of a container gasket located between the container and the container cap.

The device, called a shipper-sprayer in the industry, is sold as an integrated unit with the overcap in place enabling the insecticide manufacturer to install it on the container or bottle of liquid in a single operation in an automated bottling process. The ultimate consumer simply unscrews and discards the overcap, the pump plunger springs up and the sprayer is ready for use.

The Background of the Patent.

For many years manufacturers engaged in the insecticide business had faced a serious problem in developing sprayers that could be integrated with the containers or bottles in which the insecticides were marketed. Originally, insecticides were applied through the use of tin ***28** sprayers, not supplied by the manufacturer. In 1947, Cook Chemical, an insecticide manufacturer, began to furnish its customers with plastic pump dispensers purchased from Calmar. The dispenser was an unpatented finger-operated device mounted in a perforated cardboard holder and hung

over the neck of the bottle or container. It was necessary for the ultimate consumer to remove the cap of the container and insert and attach the sprayer to the latter for use.

Hanging the sprayer on the side of the container or bottle was both expensive and troublesome. Packaging for shipment had to be a hand operation, and breakage and pilferage as well as the loss of the sprayer during shipment and retail display often occurred. Cook Chemical urged Calmar to develop an integrated sprayer that could be mounted directly in a container or bottle during the automated filling process and that would not leak during shipment or retail handling. Calmar did develop some such devices but for various reasons they were not completely successful. The situation was aggravated in 1954 by the entry of Colgate-Palmolive into the insecticide trade with its product marketed in aerosol spray cans. These containers, which used compressed gas as a propellent to dispense the liquid, did not require pump sprayers.

During the same year Calmar was acquired by the Drackett Company. Cook Chemical became apprehensive of its source of supply for pump sprayers and decided to manufacture its own through a subsidiary, Bakan Plastics, Inc. Initially, it copied its design from the unpatented Calmar sprayer, but an officer of Cook Chemical, Scoggin, was assigned to develop a more efficient device. By 1956 Scoggin had perfected the shipper-sprayer in suit and a patent was granted in 1959 to Cook Chemical as his assignee. In the interim Cook Chemical began to use Scoggin's device and also marketed ***29** it to the trade. The device was well received and soon became widely used.

In the meanwhile, Calmar employed two engineers, Corsette and Cooprider, to perfect a shipper-sprayer and by 1958 it began to market its SS--40, a device very much similar to Scoggin's. When the Scoggin patent issued, Cook Chemical charged Calmar's SS--40 with infringement and this suit followed.

The Opinions of the District Court and the Court of Appeals.

At the outset it is well to point up that the parties have always disagreed as to the scope and definition of the invention claimed in the patent in suit. Cook Chemical contends that the invention encompasses a unique combination of admittedly old elements and that patentability is found in the result produced. Its expert testified that the invention was 'the first commercially successful, inexpensive integrated shipping closure pump unit which permitted automated assembly with a container of household ****700** insecticide or similar liquids to produce a practical, ready-to-use package which could be shipped without external leakage and which was so organized that the pump unit with its hold-down cap could be itself assembled and sealed and then later assembled and sealed on the container without breaking the first seal.' Cook Chemical stresses the long-felt need in the industry for such a device; the inability of others to produce it; and its commercial success--all of which, contends Cook, evidences the nonobvious nature of the device at the time it was developed. On the other hand, Calmar says that the differences between Scoggin's shipper-sprayer and the prior art relate only to the design of the overcap and that the differences are so inconsequential that the device as a whole would have been obvious at the time of its invention to a person having ordinary skill in the art.

***30** Both courts accepted Cook Chemical's contentions. While the exact basis of the District Court's holding is uncertain, the court did find the subject matter of the patent new, useful and nonobvious. It concluded that Scoggin 'had produced a sealed and protected sprayer unit which the manufacturer need only screw onto the top of its container in much the same fashion as a simple metal cap.' 220 F.Supp., at 418. Its decision seems to be bottomed on the finding that the Scoggin sprayer solved the long-standing problem that had confronted the industry. [FN16] The Court of Appeals also found validity in the 'novel 'marriage' of the sprayer with the insecticide container' which took years in discovery and in 'the immediate commercial success' which it enjoyed. While finding that the individual elements of the invention were 'not novel per se' the court found 'nothing in the prior art suggesting Scoggin's unique combination of these old features * * * as would solve the * * * problems which for years beset the insecticide industry.' It

concluded that 'the * * * (device) meets the exacting standard required for a combination of old elements to rise to the level of patentable invention by fulfilling the long-felt need with an economical, efficient, utilitarian apparatus which achieved novel results and immediate commercial success.' 336 F.2d, at 114.

> FN16. 'By the same reasoning, may it not also be said that if (the device) solved a long-sought need, it was likewise novel? If it meets the requirements of being new, novel and useful, it was the subject of invention, although it may have been a sort step, nevertheless it was the last step that ended the journey. The last step is the one that wins and he who takes it when others could not, is entitled to patent protection.' 220 F.Supp., at 421.

The Prior Art.

Only two of the five prior art patents cited by the Patent Office Examiner in the prosecution of Scoggin's application are necessary to our discussion, i.e., Lohse ***31** U.S. Patent No. 2,119,884 (1938) and Mellon U.S. Patent No. 2,586,687 (1952). Others are cited by Calmar that were not before the Examiner, but of these our purposes require discussion of only the Livingstone U.S. Patent No. 2,715,480 (1953). Simplified drawings of each of these patents are reproduced in the Appendix, Figs. 4--6, for comparison and description.

The Lohse patent (Fig. 4) is a shipper-sprayer designed to perform the same function as Scoggin's device. The differences, recognized by the District Court, are found in the overcap seal which in Lohse is formed by the skirt of the overcap engaging a washer or gasket which rests upon the upper surface of the container cap. The court emphasized that in Lohse '(t)here are no seals above the threads and below the sprayer head.' 220 F.Supp., at 419.

The Mellon patent (Fig. 5), however, discloses the idea of effecting a seal above the threads of the overcap. Mellon's device, likewise a shipper-sprayer, differs from Scoggin's in that its overcap ****701** screws directly on the container, and a gasket, rather than a rib, is used to effect the seal.

Finally, Livingstone (Fig. 6) shows a seal above the threads accomplished without the use of a gasket or washer. [FN17] Although Livingstone's arrangement was designed to cover and protect pouring spouts, his sealing feature is strikingly similar to Scoggin's. Livingstone uses a tongue and groove technique in which the tongue, located on the upper surface of the collar, fits into a groove on the inside of the overcap. Scoggin employed the rib and shoulder seal in the identical position and with less efficiency because the Livingstone technique ***32** is inherently a more stable structure, forming an interlock that withstands distortion of the overcap when subjected to rough handling. Indeed, Cook Chemical has now incorporated the Livingstone closure into its own shipper-sprayers as had Calmar in its SS--40.

> FN17. While the sealing feature was not specifically claimed in the Livingstone patent, it was disclosed in the drawings and specifications. Under long-settled law the feature became public property. Miller v. Brass Co., 104 U.S. 350, 352, 26 L.Ed. 783 (1882).

The Invalidity of the Patent.

Let us first return to the fundamental disagreement between the parties. Cook Chemical, as we noted at the outset, urges that the invention must be viewed as the overall combination, or--putting it in the language of the statute--that we must consider the subject matter sought to be patented taken as a whole. With this position, taken in the abstract, there is, of course, no quibble. But the history of the prosecution of the Scoggin application in the Patent Office reveals a substantial divergence in respondent's present position.

As originally submitted, the Scoggin application contained 15 claims which in very broad terms claimed the entire combination of spray pump and overcap. No mention of, or claim for, the sealing features was made. All 15 claims were rejected by the Examiner because (1) the applicant was vague and indefinite as

to what the invention was, and (2) the claims were met by Lohse. Scoggin canceled these claims and submitted new ones. Upon a further series of rejections and new submissions, the Patent Office Examiner, after an office interview, at last relented. It is crystal clear that after the first rejection, Scoggin relied entirely upon the sealing arrangement as the exclusive patentable difference in his combination. It is likewise clear that it was on that feature that the Examiner allowed the claims. In fact, in a letter accompanying the final submission of claims, Scoggin, through his attorney, stated that 'agreement was reached between the Honorable Examiner and applicant's attorney relative to limitations which must be in the claims in ***33** order to define novelty over the previously applied disclosure of Lohse when considered in view of the newly cited patents of Mellon and Darley, Jr.' (Italics added.)

Moreover, those limitations were specifically spelled out as (1) the use of a rib seal and (2) an overcap whose lower edge did not contact the container cap. Mellon was distinguished, as was the Darley patent, infra, n. 18, on the basis that although it disclosed a hold-down cap with a seal located above the threads, it did not disclose a rib seal disposed in such position as to cause the lower peripheral edge of the overcap 'to be maintained out of contacting relationship with (the container) cap * * * when * * * (the overcap) was screwed (on) tightly * * *.' Scoggin maintained that the 'obvious modification' of Lohse in view of Mellon would be merely to place the Lohse gasket above the threads with the lower edge of the overcap remaining in tight contact with the container cap or neck of the container itself. In other words, the ****702** Scoggin invention was limited to the use of a rib--rather than a washer or gasket--and the existence of a slight space between the overcap and the container cap.

[18][19] It is, of course, well settled that an invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office. Hogg v. Emerson, 11 How. 587, 13 L.Ed. 824 (1850); Crawford v. Heysinger, 123 U.S. 589, 8 S.Ct. 399, 31 L.Ed. 269 (1887). Claims as allowed must be read and interpreted with reference to rejected ones and to the state of the prior art; and claims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent. Powers-Kennedy Contracting Corp. v. Concrete Mixing & Conveying Co., 282 U.S. 175, 185--186, 51 S.Ct. 95, 99, 75 L.Ed. 278 (1930); Schriber-Schroth Co. v. Cleveland Trust Co., 311 U.S. 211, 220--221, 312 U.S. 654, 61 S.Ct. 235, 239--240, 85 L.Ed. 132 (1940).

***34** [20] Here, the patentee obtained his patent only by accepting the limitations imposed by the Examiner. The claims were carefully drafted to reflect these limitations and Cook Chemical is not now free to assert a broader view of Scoggin's invention. The subject matter as a whole reduces, then, to the distinguishing features clearly incorporated into the claims. We now turn to those features.

As to the space between the skirt of the overcap and the container cap, the District Court found:

> 'Certainly without a space so described, there could be no inner seal within the cap, but such a space is not new or novel, but it is necessary to the formation of the seal within the hold-down cap.
>
> 'To me this language is descriptive of an element of the patent but not a part of the invention. It is too simple, really, to require much discussion. In this device the hold-down cap was intended to perform two functions--to hold down the sprayer head and to form a solid tight seal between the shoulder and the collar below. In assembling the element it is necessary to provide this space in order to form the seal.' 220 F.Supp. at 420. (Italics added.)

[21] The court correctly viewed the significance of that feature. We are at a loss to explain the Examiner's allowance on the basis of such a distinction. Scoggin was able to convince the Examiner that Mellon's cap contacted the bottle neck while his did not. Although the drawings included in the Mellon application show that the cap might touch the neck of the bottle when fully screwed down, there is nothing--absolutely nothing--which indicates that the cap was designed at any time to engage the bottle neck. It is palpably evident that Mellon embodies a seal formed by a gasket compressed ***35** between the cap and the

bottle neck. It follows that the cap in Mellon will not seal if it does not bear down on the gasket and this would be impractical, if not impossible, under the construction urged by Scoggin before the Examiner. Moreover, the space so strongly asserted by Cook Chemical appears quite plainly on the Livingstone device, a reference not cited by the Examiner.

The substitution of a rib built into a collar likewise presents no patentable difference above the prior art. It was fully disclosed and dedicated to the public in the Livingstone patent. Cook Chemical argues, however, that Livingstone is not in the pertinent prior art because it relates to liquid containers having pouring spouts rather than pump sprayers. Apart from the fact that respondent made no such objection to similar ****703** references cited by the Examiner, [FN18] so restricted a view of the applicable prior art is not justified. The problems confronting Scoggin and the insecticide industry were not insecticide problems; they were mechanical closure problems. Closure devices in such a closely related art as pouring spouts for liquid containers are at the very least pertinent references. See, II Walker on Patents s 260 (Deller ed. 1937).

> FN18. In addition to Livingstone and Mellon, the Examiner cited Slade, U.S. Patent No. 2,844,290 (hold-down cap for detergent cans having a pouring spout); Nilson, U.S. Patent No. 2,118,222 (combined cap and spout for liquid dispensing containers); Darley, Jr., U.S. Patent No. 1,447,712 (containers for toothpaste, cold creams and other semi-liquid substances).

Cook Chemical insists, however, that the development of a workable shipper-sprayer eluded Calmar, who had long and unsuccessfully sought to solve the problem. And, further, that the long-felt need in the industry for a device such as Scoggin's together with its wide commercial success supports its patentability. These legal inferences ***36** or subtests do focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible of judicial treatment than are the highly technical facts often present in patent litigation. See Judge Learned Hand in Reiner v. I. Leon Co., 285 F.2d 501, 504 (2 Cir. 1960). See also Note, Subtests of 'Nonobviousness': A Nontechnical Approach to Patent Validity, 112 U.Pa.L.Rev. 1169 (1964). Such inquiries may lend a helping hand to the judiciary which, as Mr. Justice Frankfurter observed, is most ill-fitted to discharge the technological duties cast upon it by patent legislation. Marconi Wireless Telegraph Co. of America v. United States, 320 U.S. 1, 60, 63 S.Ct. 1393, 87 L.Ed. 1731 (1943). They may also serve to 'guard against slipping into use of hindsight,' Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co., 332 F.2d 406, 412 (1964), and to resist the temptation to read into the prior art the teachings of the invention in issue.

However, these factors do not, in the circumstances of this case, tip the scales of patentability. The Scoggin invention, as limited by the Patent Office and accepted by Scoggin, rests upon exceedingly small and quite non-technical mechanical differences in a device which was old in the art. At the latest, those differences were rendered apparent in 1953 by the appearance of the Livingstone patent, and unsuccessful attempts to reach a solution to the problems confronting Scoggin made before that time became wholly irrelevant. It is also irrelevant that no one apparently chose to avail himself of knowledge stored in the Patent Office and readily available by the simple expedient of conducting a patent search--a prudent and nowadays common preliminary to well organized research. Mast, Foos & Co. v. Stover Mfg. Co., 177 U.S. 485, 20 S.Ct. 708, 44 L.Ed. 856 (1900). To us, the limited claims of the Scoggin patent are clearly evident from the prior art as it stood at the time of the invention.

***37** We conclude that the claims in issue in the Scoggin patent must fall as not meeting the test of s 103, since the differences between them and the pertinent prior art would have been obvious to a person reasonably skilled in that art.

The judgment of the Court of Appeals in No. 11 is affirmed. The judgment of the Court of Appeals in Nos. 37 and 43 is reversed and the cases remanded to the District Court for disposition not inconsistent with this opinion. It is so ordered.

Judgment of Court of Appeals in No. 11 affirmed. Judgment of Court of Appeals in Nos. 37 and 43 reversed and cases remanded to District Court.

Mr. Justice STEWART took no part in the consideration or decision of Nos. 37 and 43.

Mr. Justice FORTAS took no part in the consideration or decision of these cases.

APPENDIX TO OPINION OF THE COURT.
FIGURE 1.-GRAHAM '798 PATENT

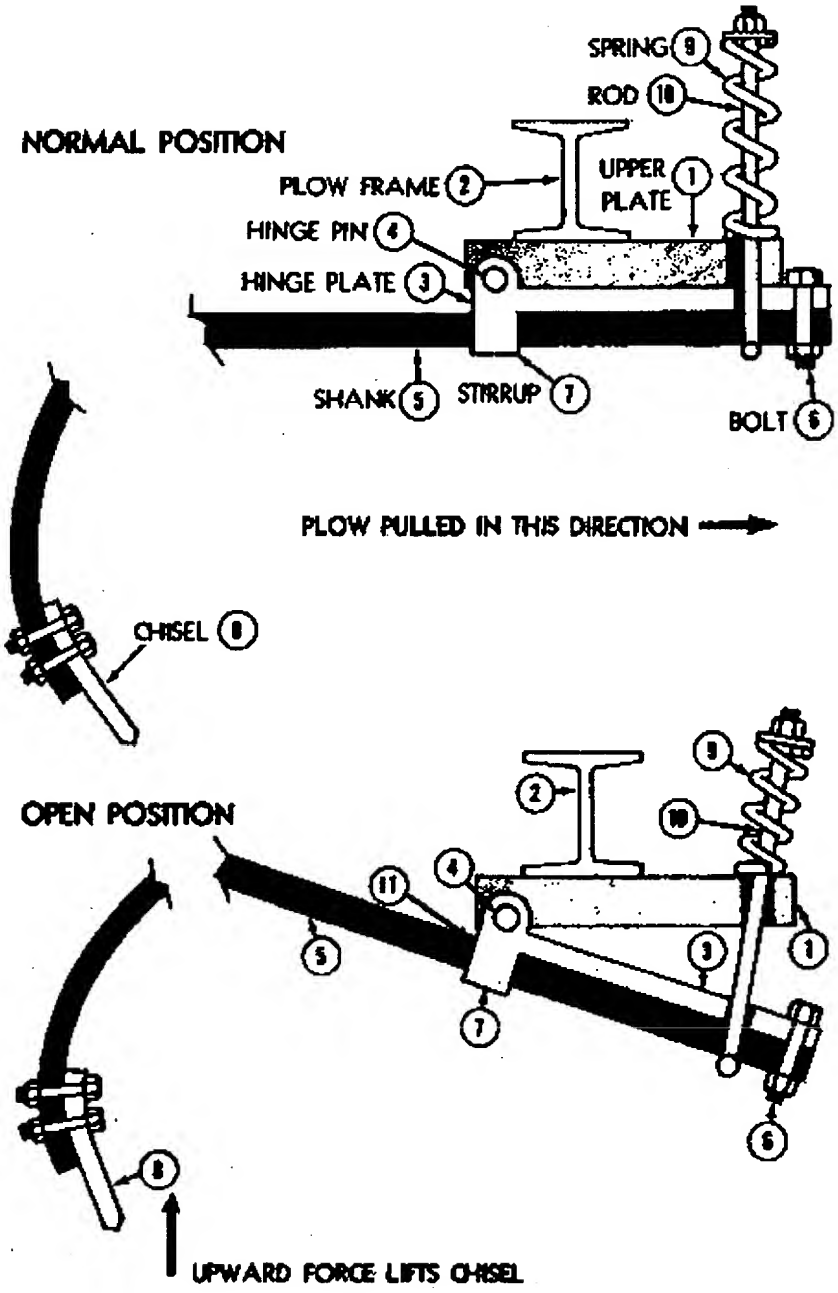
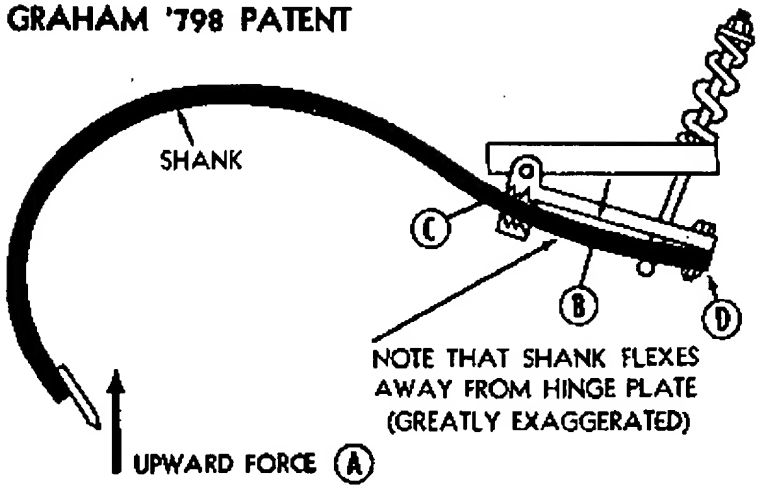


FIGURE 2.-FLEX COMPARISON



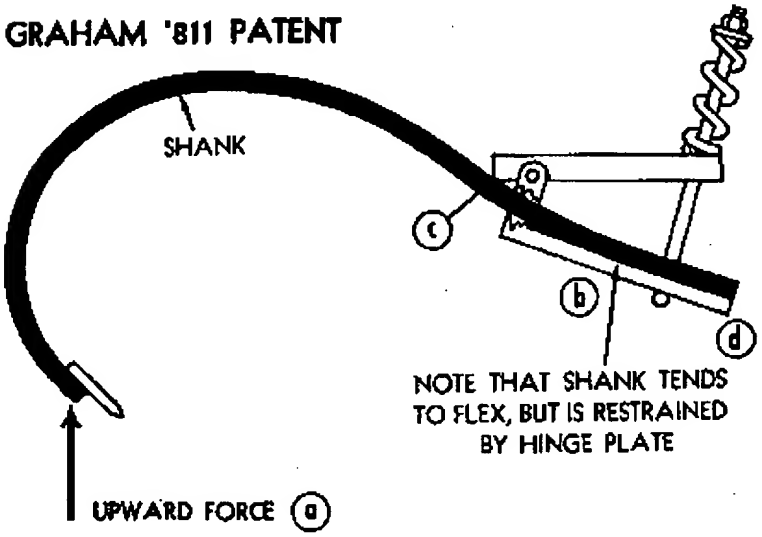


FIG. 3. SCOGGIN PATENT 2,870,943

(The Patent in Issue)

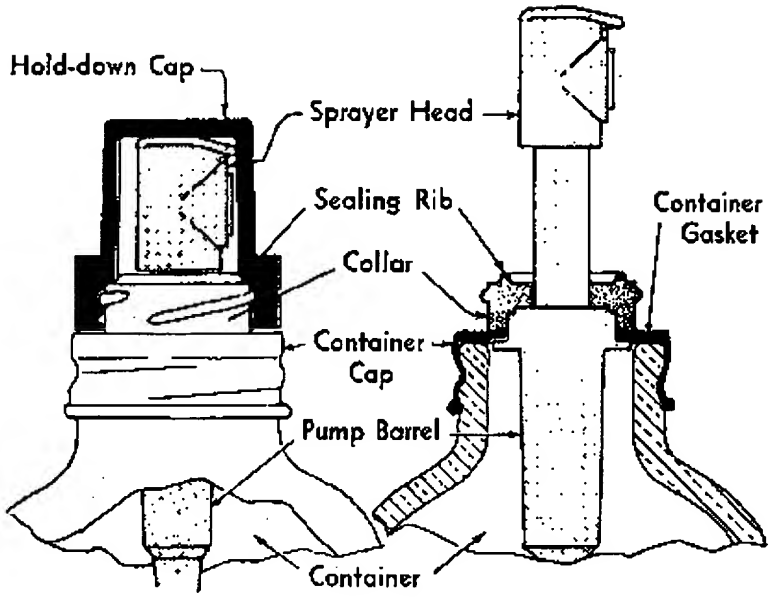


FIG. 5. MELLON PATENT 2,586,687

(Prior art 1952)

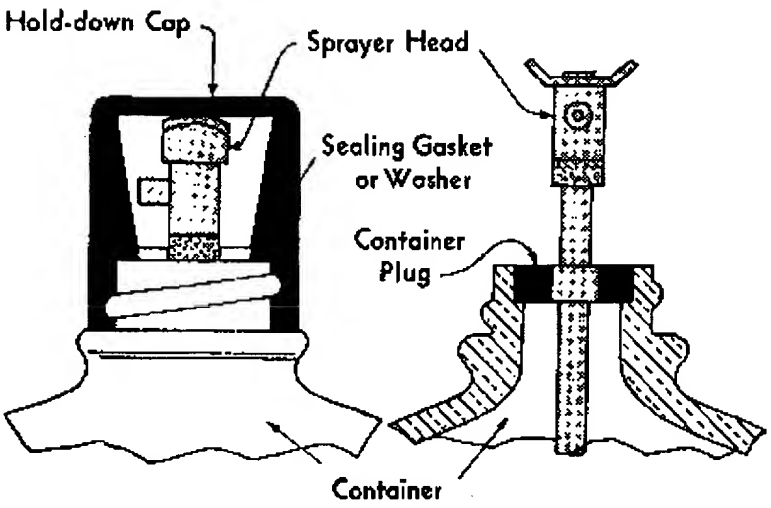


FIG. 4. LOHSE PATENT 2,119,884

(Prior art 1938)

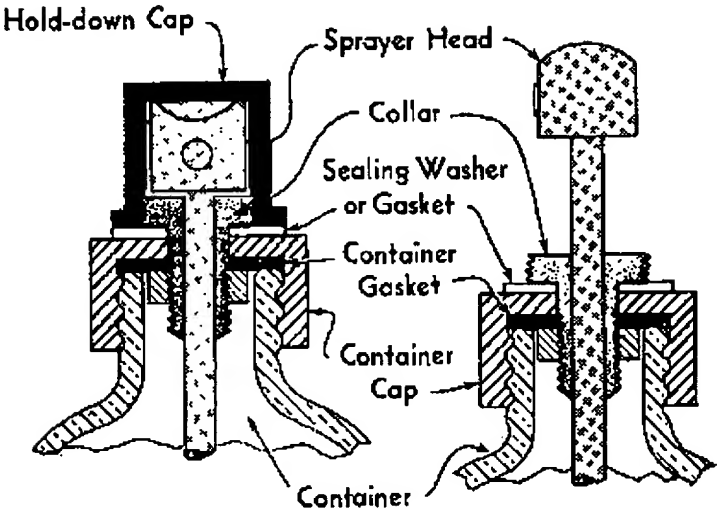
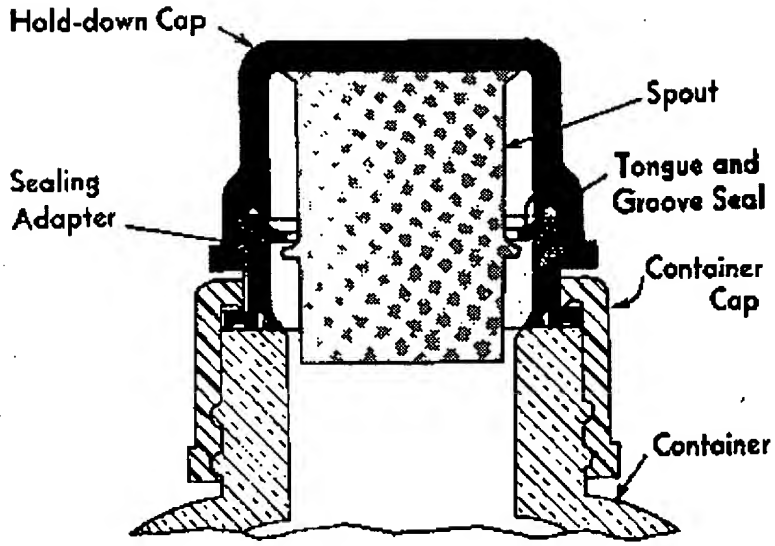


FIG. 6. LIVINGSTONE PATENT 2,715,480

(Prior art 1953)



Briefs and Other Related Documents (Back to top)

• 1965 WL 115658 (Appellate Brief) Brief for Respondent (Sep. 22, 1965)

• 1965 WL 115659 (Appellate Brief) Brief for Petitioner (Aug. 23, 1965)

• 1965 WL 115657 (Appellate Brief) Brief on Behalf of Respondents (Mar. 30, 1965)

• 1965 WL 115656 (Appellate Brief) Brief for the New York Patent Law Association as Amicus Curiae (Mar. 04, 1965)

• 1965 WL 130090 (Appellate Brief) Brief, Amicus Curiae. (Mar. 04, 1965)Original Image of this Document with Appendix (PDF)

• 1965 WL 130089 (Appellate Brief) Brief on Behalf of American Bar Association, Amicus Curiae (Mar. 03, 1965)Original Image of this Document (PDF)

• 1965 WL 115655 (Appellate Brief) Brief Amicus Curiae in Support of 35 USC 103 (Mar. 02, 1965)

• 1965 WL 115654 (Appellate Brief) Amicus Curiae Brief Of The Patent, Trade-Mark And Copyright Section Of The State Bar Of Texas (With The Consent Of The Board Of Directors Of The State Bar Of Texas) (Feb. 26, 1965)

END OF DOCUMENT

L11 ANSWER 7 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001129199 EMBASE
TITLE: [Non-viable myocardium, documented by TL-201 SPECT, is a main determinant of the increase in the secretion of cardiac natriuretic peptides].
LE MYOCARDE "NON VIABLE", DETECTE PAR LA TOMOSCINTIGRAPHIE AU TL-201, EST UN DETERMINANT ESSENTIEL DE L'AUGMENTATION DE LA SECRETION DES PEPTIDES NATRIURETIQUES CARDIAQUES.
AUTHOR: Hassan N.; Mertes P.M.; Mercenier C.; Olivier P.; Djaballah K.; Claudon O.; De Talance N.; Marie P.Y.; Grentzinger A.; Karcher G.; Bertrand A.
CORPORATE SOURCE: Dr. N. Hassan, Service de Medecine Nucleaire, Hopital de Brabois, 54500 Vandoeuvre, France. n.hassan-sebbag@chu-nancy.fr
SOURCE: Medecine Nucleaire, (2000) 24/6 (301-310).
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ISSN: 0928-1258 CODEN: MNIMEX
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DOCUMENT TYPE: Journal; Article
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023 Nuclear Medicine
037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: English; French
AB **Cardiac** natriuretic peptides are strong prognostic indicators in chronic **heart** failure. However, in patients with coronary artery disease (CAD), it is not known whether the increase in their secretions is triggered by the presence of **necrotic** or **ischemic myocardium**, both situations being able to induce a **cardiac** dysfunction. The plasma concentrations of **BNP** and ANP were determined at rest and at exercise in 58 CAD patients who underwent exercise TL-201 SPECT. Areas with predominantly **necrotic** ("non viable") myocardium were documented by TL-201 SPECT in 20 patients and their presence was associated with: 1) higher plasma levels at rest for **BNP** (in ng/l: 111 .+-. 152 vs 26 .+-. 27, p = 0,001) and ANP (in ng/l: 46 .+-. 54 vs 21 .+-. 18, p = 0,01). 2) higher increases between rest and exercise for **BNP** (in ng/l: + 19 .+-. 20 vs +6 .+-. 7, p = 0,001) but not for ANP (in ng/l: + 41 .+-. 55 vs +25 .+-. 25, NS). However, **ischemic myocardium**, documented at exercise-SPECT in 22 patients, was totally unrelated to the plasma levels of **BNP** and ANP at rest, and to their increases at exercise. By multivariate analysis, the extent of **necrotic myocardium** and patients age were the best independant predictors of **BNP** and ANP concentrations at rest. In patients with CAD, the increase in the plasma levels of **BNP** and ANP : 1) is mainly related to the presence of **necrotic myocardium**, 2) also depends on patients age, 3) but is not triggered by the presence of **ischemic myocardium**.

Non-viable myocardium, documented by TL-201 SPECT.
is a main determinant of the increase in the secretion of cardiac natriuretic peptides

ABSTRACT

Cardiac natriuretic peptides are strong prognostic indicators in chronic heart failure. However, in patients with coronary artery disease (CAD), it is not known whether the increase in their secretions is triggered by the presence of necrotic or ischemic myocardium, both situations being able to induce a cardiac dysfunction.

The plasma concentrations of BNP and ANP were determined at rest and at exercise in 58 CAD patients who underwent exercise TL-201 SPECT. Areas with predominantly necrotic (non-viable) myocardium were documented by TL-201 SPECT in 20 patients and their presence was associated with:

1) higher plasma levels at rest for BNP (in ng/l: 111 ± 152 vs 26 ± 27, p = 0,001) and ANP (in ng/l: 46 ± 54 vs 21 ± 18, p = 0,01).

2) higher increases between rest and exercise for BNP (in ng/l: +19 ± 20 vs +6 ± 7, p = 0,001) but not for ANP (in ng/l: +41 ± 55 vs +25 ± 25, NS).

However, ischemic myocardium, documented at exercise-SPECT in 22 patients, was totally unrelated to the plasma levels of BNP and ANP at rest, and to their increases at exercise.

By multivariate analysis, the extent of necrotic myocardium and patients age were the best independent predictors of BNP and ANP concentrations at rest.

In patients with CAD, the increase of the plasma levels of BNP and ANP:
1) is mainly related to the presence of necrotic myocardium,
2) also depends on patients age,
3) but is not triggered by the presence of ischemic myocardium.

INTRODUCTION

In coronary disease, the plasmatic dosage of cardiac natriuretic peptides are utilized more and more frequently to allow an early diagnosis in types of CAD with little or no symptoms *[1, 2]* and above all, to evaluate the seriousness of the disease because the plasma concentrations of these peptides appear strongly related to the risk of cardiac death. In answer to an augmentation of the tension of the cardiac walls, the myocytes secrete these peptides, principally at the atrium level for the Type A peptide (atrial natriuretic peptide = ANP) and ventricle level for the Type B peptide (brain natriuretic peptide = BNP) *[6-8]*. Thus, during insuffisance cardiac, the volumetric and/or barometric surcharge of the cardiac cavities is responsible for the BNP and ANP secretion increase. This has favorable consequences as these peptides are antagonists of the renal-angio-tensine-aldosterone system and have diuretic, natriuretic and vasodilating effects *[7-9]*. In chronic insuffisance cardiac, there is a strong correlation between the severity of the left ventricle dysfunction and the plasma concentrations in ANP and in BNP

[8-10]. However, in coronary patients, it is not known whether the increase in the plasma concentrations in those peptides is triggered not only by the presence of necrotic myocardium but also by ischemic myocardium as both situations can be responsible for cardiac dysfunction.

The objective of our study was to determine, in CAD patients, the determining factors causing the increase of plasma concentrations of the natriuretic, cardiac peptides. Particularly, in using the results obtained in exercise TL-201 SPECT and at rest we have analyzed correlations between: 1) ischemia and consequences of myocardial infarction, 2) concentrations of natriuretic cardiac peptides at rest and at exercise.

MATERIALS AND METHODS

Study Group Selection

We have prospectively included 58 patients for testing at exercise TSM and for a cardiac angioscintigraphy, presenting proven antecedents of coronary disease (myocardial infarction and/or coronary stenoses significant in coronarography) and having consented to participate in this study.

The criteria of exclusion were as follow:

1) severe renal insufficiencies, 2) arterial hypertension not controlled by medical treatment, 3) cardiac arythmia caused by auricular fibrillation, 4) presence of a congenital, hypertrophic or valvular cardiopathy (significant valvular narrowing or leak of grade I to II), 5) presence of a primitive dilated cardiomyopathy. The purpose of the exclusion criteria was to eliminate other pathologies that could induce an increase of secretion in the natriuretic cardiac peptides *[7-9]*.

Myocardial Tomoscintigraphies TL-201

The experiment at exercise was performed on an ergonomic bicycle. The exercise began at 20 W and was progressively increased stepwise by 20 W at every two minutes. A simultaneous recordation of the 12 electrocardiographic derivations was performed each minute and derivations V_1, V_5 and aVF were recorded continuously. The criteria for stopping the experiment at exercise were as follows: physical exhaustion, theoretical maximal frequency achieved (calculated according the following formula: 220 – age), apparition of an angina or of a ST-depression at 2 mm of the ST segment, caused at exercise by a ventricular tachycardia, a systematic arterial hypertension, or a low blood pressure.

An activity equaled to 37 TL-201 MBq by 25 kg in body weight was injected intravenously one minute before the end of the exercise. The tomographic acquisitions at exercise began 10 min after the injection of the TL-201 and those at rest, 3 to 5 hours later, 1 hour after the re-injection at rest of an activity equaled to one-third of the quantity administered at exercise *[11-13]*.

The acquisitions were performed in prone position if the patient could tolerate this position, and in supine position if otherwise. The tomoscintingraphic techniques have already been described *[11-13]* and comprise the recordation of 32 images lasting 40 seconds each, at 180 degrees. These recordings were performed with a double-header camera (DST-XL, Sopha Medical Vision), equipped with a low energy, very high resolution collimator, and with two 20% windows centered on the peaks at 80 keV and 167 keV of the TL-201. The images were re-built by filtered retro-projection (Hamming-Hann filter) and the tests were analyzed by 8 mm thick joint sections, oriented in three directions: small axis, large horizontal axis, and grand vertical axis sections.

The tomoscintigraphic sections were analyzed in consensual manner by two experimented technicians, using the left ventricle divided in 20 segments and fixation score in four levels: 0, normal fixation; 1, slight diminution of fixation; 2, net diminution of fixation; 3, severe diminution of fixation *[11-13]*.

The extent of the anomalies from the perfusion at exercise were calculated according to the percentage of segments having a fixation score higher than 1 on the acquisitions at exercise. The extent of the perfusion (ischemia territories) reversible anomalies was calculated according to the percentage of the areas with fixation score higher than 1 on the experiment at exercise and decreased by at least one point on the experiment at rest.

The extent of the irreversible lacuna was calculated according to the percentage of the segment from which the fixation score was higher than 1 on the experiment at exercise presenting no decrease on the experiment at rest. Lastly, the extent of necrotic myocardium, which corresponds to myocardial tissue with necrotic disposition, was calculated according to the percentage of segments included in an irreversible lacuna and for which the fixation score, analyzed on acquisitions at rest, were less than 50% of the maximum fixation of the left ventricle *[13]*. This 50% level was easily identifiable with the colored scale utilized, it corresponded to the transition between green (fixation inferior by 50%) and the inclusion in variable proportion in yellow (fixation superior by 50%).

Cardiac Angioscintigraphy

Cardiac angioscintigraphy was performed at rest, after intravenous injection of 600 to 700 MBq of albumine marked with ^{99m}Tc. According to a previously described technique *[14]*, the acquisition was performed with a high sensitivity collimator with left anterior oblique incidence with an obliquity degree permitting the best possible separation between the two ventricles. Sixteen images per cardiac cycle were recorded and the acquisition was stopped when, in average, 350,000 counts per image were obtained. Areas of systolic and diastolic interest of the left ventricle were manually traced; the area of interest corresponding to the measure of the background noise was placed on the inferolateral edge of the segment of diastolic interest. The fraction of the ejection of the left ventricle was calculated according to the formula: (AD-AS)/AD, where AD and AS represent left ventricle activities determined respectively in diastole and systole, after subtracting the activity corresponding to the background noise.

Plasma Concentration Measurement of Natriuretic Cardiac Peptides

Samples were obtained with a desilet placed in a forearm vein, the thallium injection was performed at the level of the superior controlateral limb. Three samples were obtained, the first at rest (immediately before the beginning of the exercise), the second at the maximum activity level of exercise (during the minute following the thallium injection), and the third during recuperation (20 min after the end of the exercise). The samples were collected in polyethylene tubes containing EDTA and aprotinine (500 U/ml). They were then preserved in ice until their arrival in the laboratory where, after immediate centrifugation, the plasma was frozen at -70°C. The dosage of BNP and ANP was determined by immunoradiometric techniques without preliminary extraction, using two monoclonal antibodies according to the manufacturers' instructions (bio international CIS kit, established technique from the Japanese company, Shionogi *[9, 15]*.

Statistic Analysis

The quantitative parameters were calculated as average (± ecart-type) and were compared to non-parametric tests: a Wilcoxon test was used for paired series and a Mann-Whitney test was used for comparisons between non-paired series. A value of $p > 0.05$ was considered a significant difference. A multivariate linear regression analysis was performed step-by-step in ascending manner (Statview TM II, Abacus Concepts, Berkeley).

Table I.
Patients Characteristics

Clinical Facts	
Age (years)	60 ± 10
Sex (female)	5 pts (9%)
History	
- coronary revascularization	35 pts (61%)
- myocardial infarction	44 pts (6%)
- wave Q on EKG	39 pts (67%)
- anterior wave Q	17 pts (29%)
Risk Factors	
- arterial hypertension	15 pts (26%)
- dyslipidemy	6 pts (10%)
- diabetes	
Symptoms	
- angina	26 pts (45%)
- dyspny (class NYHA = II)	9 pts (15%)
Treatment Taken on Day of Test	
β-blockers	32 pts (55%)
Calcic inhibitors	8 pts (14%)
Nitrate Derivatives or Molsidomine	14 pts (24%)
Conversion enzyme inhibitor	24 pts (41%)
Diuretics	3 pts (5%)

(pts = patients)

RESULTS

Patients Characteristics and Radiosotopic Exam Results

The principal characteristics of the patients are detailed in Table I. The studied group was comprised of 53 men and 5 women and the average age was 60 years old. A pre-condition of myocardial infarction was found in 76% of the patients and 67% displayed wave Q on the EKG.

Only 15% of the patients displayed disabling dyspny (class = II according to the New-York Heart Association classification).

The results of the experiments at exercise, the TSM and the cardiac angioscintigraphies are detailed in Table II.

The experiment at exercise was positive (thoracic pain or ST-depression at 1 mm of the ST segment) in 22% of the patients. The TSM displayed signs of ischemic myocardium (reversible lacuna > 5% of the VG) in 22 cases (38%), and myocardial segments with necrotic predominance (non-viable myocardia > 5% of VG) in 20 cases (34%). The simultaneous presence of ischemic myocardium (> at 5% of the VG) and of an area with necrotic predominance (> at 5% of the VG) was observed in 9 patients (15%). Thus, 13 patients presented ischemia but without areas with necrotic predominance, and 11 presented cases of reversed situation (area with necrotic predominance but no ischemia). In cardiac angioschintigraphy, the ejection fraction of the left ventricle was 0,56 in average and only 22% of the patients had an abnormal value (< 0,50).

Table II.
Results of Experiment at Exercise, TSM TL-201 SPECT, and Cardiac Angioscintigraphy

Experiment At Exercise	
Maximum Effort (W)	126 15
Cardiac frequency at rest (bpm)	76 ± 15
Maximum cardiac frequency (bmp)	129 ± 24
Maximum systolic arterial tension (mmHg)	180 ± 32
Maximum double product (x 100)	236 ± 72
Angina or ST-depression = 1 mm of ST segment	13 pts (34%)
Myocardial tomoscintigraphies	
Presence of ischemic myocardia	23 pts (38%)
Presence of non-viable myocardia	20 pts (34%)
Extent of lacunas (% of VG)	
- lacuna at exercise	18 ± 18
- reversible lacuna	8 ± 8
- irreversible lacuna	11 ± 15
- non-viable myocardia	8 ± 13
Cardiac angioscintigraphy	
Ejection fraction of VG	0,56 ± 0,12
Ejection fraction < 0,50	13 pts (22%)

(pts = patients).

Table III.
Evolutions of paired ANP and BNP plasma concentrations (in ng/l), at rest, at maximum exercise, then 20 min later, and during recuperation

Rest	Exercise	Recuperation		Value of p	
(1)	(2)	(3)	1 vs 2	2 vs 3	3 vs 3
ANP 30 ± 37	59 ± 56	51 ± 48	0,0001	0,03	0,0001
BNP 56 ± 100	66 ± 112	62 ± 111	0,0001	0,0003	0,0001

Evolution at exercise of plasma concentrations in ANP and BNP

For each of the two peptides, the concentrations measured at exercise were more significant than those measured at rest (Table III). However, this increase at exercise was much more pronounced for ANP than for BNP (in % of the initial values at rest: +151 ± 160 % vs + 37 ± 60%, p = 0,0001).

Comparatively to the measures obtained at exercise, those obtained during recuperation, 20 min later, were slightly but importantly lower and this for ANP as well as for BNP (Table III).

Influences of ischemia, necrotic myocardium, and left ventricle dysfunction

Plasma concentrations in peptides were compared between patients with ischemic myocardium in TSM (n = 22) and those without ischemic myocardium (n = 36). The results are detailed in Table IV and illustrated in Figure 1. For each of the two peptides, there was no significant difference and this, in measured concentrations at rest, at exercise, and during the recuperation phase as well as in concentration variations at rest and at exercise. Peptide plasma concentrations were also compared between patients with myocardial segments of necrotic predominance in TSM (n = 20) and those who did not have myocardial areas (n = 38). The results are detailed in Table IV and illustrated in Figure 2. For each of the two peptides, the presence of these necrotic segments were associated with greater plasma concentrations and this, at rest, at exercise, or during recuperation. Further, peptide concentration increases between rest and exercise (difference of the concentrations between rest and exercise) were greater in patients with necrotic myocardial segments, this correlation was significant for BNP but not for ANP.

Results remained the same when patients having non viable regions and ischemia were excluded from analysis. Lastly, plasma concentrations of peptides were compared between patients with an ejection fraction abnormally low in cardiac angioscintigraphy (< 0,50; n = 13) and those without such condition (n = 45).

Results are detailed in Table III. For each of the two peptides, the presence of an ejection fraction < 0,50 was linked to concentrations greater at rest, at maximum exercise as well as during recuperation. Further, the increase of the concentration in BNP between at rest and at exercise was greater for patients with an ejection fraction < 0,50.

As previously, results remained the same when patients with necrotic segments and ischemia were excluded from the analysis.

Table IV.
Development of concentrations in ANP and BNP (in mg) in relation to the presence or absence 1) of necrotic myocardial segments, 2) of ischemic activity and 3), of an abnormal ejection fraction < 0,50.

		Non-Viable Myocardium			Activity Ischemia			Ejection Fraction		
		Present (n = 20)	Absent (n = 38)	P	Present (n = 22)	Absent (n = 36)	P	< 0,50 (n = 13)	± 0,50 (n = 45)	P
ANP	rest	46 ± 54	21 ± 18	0,01	30 ± 37	30 ± 36	NS	61 ± 64	21 ± 18	0,0001
	exercise	86 ± 80	45 ± 32	0,01	63 ± 55	57 ± 58	NS	89 ± 75	51 ± 48	0,04
	recuperation	73 ± 63	39 ± 33	0,01	51 ± 45	50 ± 51	NS	85 ± 69	42 ± 37	0,004
	increase at exercise	41 ± 55	25 ± 25	NS	35 ± 34	28 ± 41	NS	30 ± 31	30 ± 41	NS
BNP	rest	111 ± 53	26 ± 27	0,001	49 ± 65	59 ± 116	NS	166 ± 81	27 ± 22	0,001
	exercise	130 ± 171	32 ± 30	0,001	49 ± 65	59 ± 116	NS	166 ± 181	27 ± 22	0,001
	recuperation	125 ± 171	30 ± 30	0,001	59 ± 94	65 ± 122	NS	185 ± 202	31 ± 26	
	increase at exercise	19 ± 20	6 ± 7	0,001	10 ± 10	11 ± 17	NS	22 ± 25	8 ± 8	0,003

NS: non significant

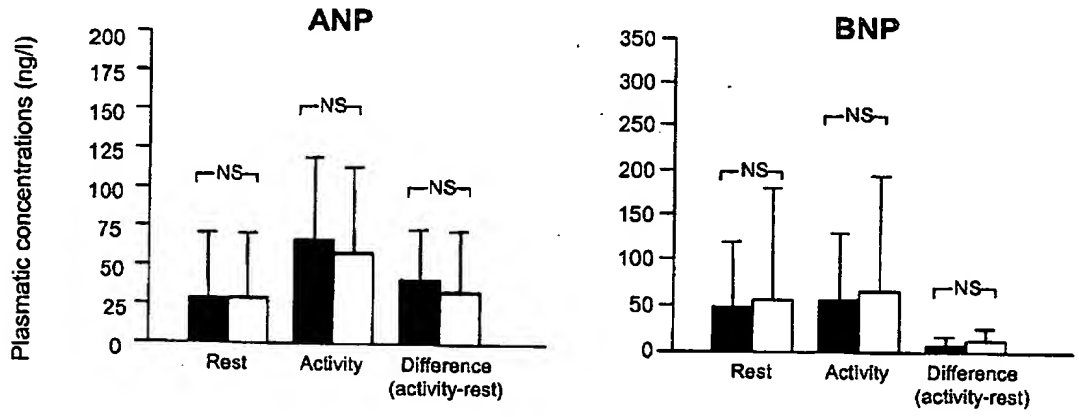

Figure 1. Comparison of plasma concentrations in peptides measured at rest and at exercise, as well as of the concentration differences between at rest and during exercise, between patients having (black columns) and those not having (white columns) ischemic myocardium. (* = p < 0,05, NS = non significant)

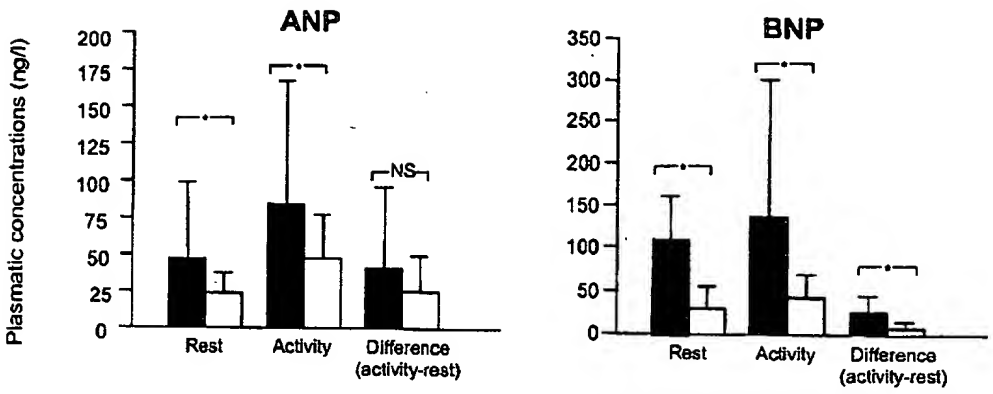

Figure 2. Comparison of plasma concentrations in peptides measured at rest and at exercise, as well as of the concentration differences between at rest and during exercie, between patients having (black columns) and those not having (white columns) necrotic myocardial areas (non-viable myocardium).
(* = $p < 0,05$, NS = non significant)

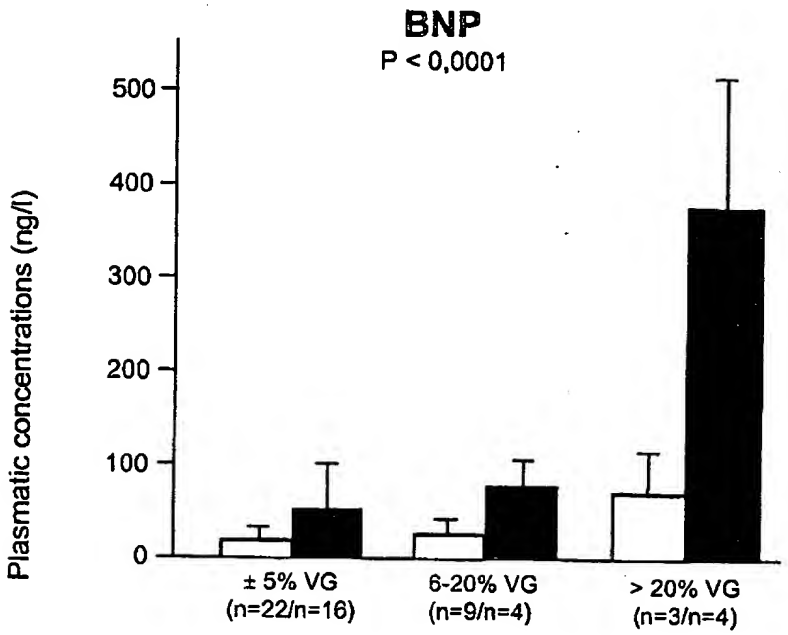

Figure 3. Apportionnement of plasma concentrations in BNP in function:
1) of the extent of necrotic myocardium (non-viable), apportioned in 3 categories,
2) of the age of the patients, apportioned in 2 categories: <60 ans (white columns) and = 60 years (black columns)

Multivariate Analyses

Multivariate analyses were performed in order to search for the best predictor parameters independently of plasma concentrations in peptides at rest.

For each of the two peptides, this analysis was performed by including all clinical and para-clinical parameters listed in Tables I and II.

The best independent predictor parameters of plasma concentrations in BNP at rest were: the extent of necrotic myocardium ($p < 0,0001$) and the age of the patient ($p < 0,0001$); and in ANP, these parameters were: the extent of necrotic myocardium ($p = 0,01$), age of the patients and the cardiac frequency at rest ($p = 0,04$).

For each of the two peptides, this analysis was performed in including all clinical and para-clinical parameters listed in Tables I and II.

The best independent predictor parameters of plasma concentrations in BNP at rest were: the extent of necrotic myocardium ($p < 0,0001$) and the age of the patient ($p < 0,0001$); and for ANP, these parameters were: the extent of necrotic myocardium ($p = 0,01$), the age of the patients ($p < 0,0001$) and the cardiac frequency at rest ($p = 0,04$).

After exclusion of the tomoscintigraphic parameters, the ejection fraction value of the VG was selected instead of the extent of necrotic myocardium, other parameters selected being unchanged.

Figure 3 illustrates these results in showing the double dependency of plasma concentrations at rest in BNP, vis-à-vis:

1) the extent of necrotic myocardium,
2) the age of the patients.

DISCUSSION

In chronic cardiac failure, there is a strong correlation between the severity of left ventricle dysfunction and plasma concentrations of these peptides *[8-10]*.

However, in coronary patients, very different physiopathologic situations are susceptible to induce left ventricle dysfunction. It is regarding the presence of traumatisms of the infarction, but also of ischemic myocardium, the beginning of which generates contractility anomalies which can be resolved or evolve towards chronicity (hibernating myocardium *[16]*, repeated myocardial sideration.

In coronary patients, it is still not known if the increase of cardiac natriuretic peptide secretion can be triggered not only by the presence of necrotic but also ischemic myocardial areas.

TSM of exercise TL-201, as performed with the re-injection technique at rest, allows very precise information on the extent of the severity of ischemic myocardium *[11, 18]*, as well as on the importance of irreversible traumatisms of the infarction ("non-viable" myocardium) *[13, 21]*.

In our study, we have researched the correlations between these tomoscintigraphic parameters and the plasmatic levels of ANP and BNP, in order to evaluate the respective roles of ischemic and necrotic myocardium, in the increase of peptide secretion.

Evolution at exercise of the cardiac natriuretic peptide concentrations

In the group analyzed, we have observed that concentrations in BNP and ANP were increased at exercise, and that this increase was much more significant in ANP than in BNP.

Similar observations were already made in a group of patients with cardiac failure *[21-24]*. The concentration increases at exercise is generally explained by the release of peptides from the intramyocytaire storage granules, and these granules have the characteristic of containing more ANP than BNP *[23, 24]*.

On the other hand, in our study, a decrease of plasma concentrations was visible as soon as during the 20th minute following the end of the exercise, which is consistent with studies in the literature and explicable by the short plasmatic half-lives (22 min) *[25]* of BNP and specially ANP (2 to 3 min) *[26]*.

The impact of necrotic myocardium and the age of patients

The principal result of this study is the relation between plasmatic concentrations in peptides and the extent of the necrotic myocardial areas.

The relation is particularly significant for concentrations measured at rest, the multivariate analysis having shown that the extent of necrotic myocardium was a predictive parameter probably more significant than the value of the ejection fraction of the left ventricle. Of course, this does not mean that the necrotic areas are directly responsible for the increase in secretion.

However, we can infer that this increase is produced in non-necrotic segments, because these are submitted to a volumetric and/or barometric surcharge becoming greater as the necrotic areas are extended.

There is also a relation quite significant between the presence of necrotic myocardium and the importance of the increase, at exercise, of plasmatic concentrations in BNP. This observation, could, again, be explained by the release mechanism of peptides at exercise from the intramyocytaire storage granules. In fact, studies have shown that there is a significant relation between the severity of left ventricle dysfunction and the importance of the intramyocytaire storage in ANP and BNP *[27]* measured on biopsies.

Thus, patients having cardiac dysfunction and traumatisms of infarction, could be, not only those with the highest elevations of peptide concentrations at rest, but also those for which exercise, in triggering the release of important intramyocitaire storages, generate the most significant plasma concentration increases.

However, the results of multivariate analyses also showed that the age of patients significantly affected plasmatic concentrations in peptides. More precisely, for a determined severity of the traumatisms of infarction, we have observed that plasmatic concentrations in peptides were clearly more significant in older patients.

This relation regarding age has already been demonstrated in a certain number of studies in healthy subjects or with cardiac deficiency.

Actually, it is not known if this phenomenon is linked to the aging process of the organism (decrease in compliance and elasticity of cardiac walls) and which could increase the mechanical stimulus responsible for secreting BNP and ANP (increase of parietal tension). It is also possible that the aging process occurs with an increase of secretory response to this mechanical stimulus.

Our results show that it is probably important to consider the age of the patients when levels of BNP and ANP are used to detect or evaluate the severity of cardiac deficiency.

Absence of impact of myocardial ischemia

We have observed no impact of ischemic myocardium, such as can be objectified in exercise TSM, on plasmatic concentrations in peptides.

Yet, ischemia causes contractility anomalies at times severe and susceptible to become chronic (myocardial hibernation linked to a chronic ischemia *[16]*, repeated myocardial sideration linked to intermittent periods of myocardial ischemia *[17]*).

The results of our study demonstrated that ischemic myocardium has no impact on peptide concentrations at rest nor on their increases at exercise.

Other studies will probably be necessary to appreciate the impact of ischemia when conditions are such that it is associated and/or responsible for a more severe left ventricle dysfunction (only 13 patients had an ejection fraction less than 50%).

Be that as it may, our studies demonstrate that ischemic myocardium cannot be detected in measuring plasma concentrations in cardiac natriuretic peptides, at rest and at exercise.

Variations in function of the selected peptide

We have observed that plasma concentrations at rest in BNP had a greater correlation than those in ANP, to the extension of the necrotic areas.

On the other hand, according to the multivariate analysis results, concentrations at rest in ANP vary, not only in function of age and extension of necrotic areas, but also in function of the cardiac frequency, which is not the case with concentrations at exercise in BNP.

Numerous studies have shown that concentrations in ANP were more variable that those of BNP because they are more dependent on the hemodynamic conditions of the sample (cardiac frequency, posture *[21, 22, 29]*. This is partly caused, on one hand, by a plasmatic half-life much shorter in ANP (2 to 3 min *[26]*) than in BNP (22 min *[25]*), which implies that plasmatic concentrations in ANP are susceptible to decrease much more rapidly than those in BNP.

On the other side, because intramyocytaire storage granules contain much more ANP than BNP *[23, 24]*, the release of these storages, which we know can be triggered by a simple increase of cardiac frequency *[21, 22, 29]*, can induce elevated concentrations much more pronounced for ANP than for BNP. This last point is further illustrated by our observation, at exercise, that the plasmatic concentrations in ANP increase much more than those in BNP.

CONCLUSION

This study of coronary patients demonstrate that the extension of necrotic myocardium is the essential determining factor of plasma concentration increases in ANP and above all in BNP. However, in those patients, the presence of ischemic myocardium does not seem to be able to trigger those concentration increases.

Lastly, these peptide concentrations vary also in function of age which is, thus, a parameter to consider during clinical studies.

SUMMARY

Non-viable myocardium, documented by TL-201 SPECT.
is a main determinant of the increase in the secretion of cardiac natriuretic peptides

Cardiac natriuretic peptides are strong prognostic indicators in chronic heart failure. However, in patients with coronary artery disease (CAD), it is not known whether the increase in their secretions is triggered by the presence of necrotic or ischemic myocardium, both situations being able to induce a cardiac dysfunction.

The plasma concentrations of BNP and ANP were determined at rest and at exercise in 58 CAD patients who underwent exercise TL-201 SPECT. Areas with predominantly necrotic (non-viable) myocardium were documented by TL-201 SPECT in 20 patients and their presence was associated with:

1) higher plasma levels at rest for BNP (in ng/l: 111 ± 152 vs 26 ± 27, p = 0,001) and ANP (in ng/l: 46 ± 54 vs 21 ± 18, p = 0,01).

2) higher increases between rest and exercise for BNP (in ng/l: +19 ± 20 vs +6 ± 7, p = 0,001) but not for ANP (in ng/l: +41 ± 55 vs +25 ± 25, NS).

However, ischemic myocardium, documented at exercise-SPECT in 22 patients, was totally unrelated to the plasma levels of BNP and ANP at rest, and to their increases at exercise.

By multivariate analysis, the extent of necrotic myocardium and patients age were the best independent predictors of BNP and ANP concentrations at rest.

In patients with CAD, the increase of the plasma levels of BNP and ANP:
1) is mainly related to the presence of necrotic myocardium,
2) also depends on patients age,
3) but is not triggered by the presence of ischemic myocardium.

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N-Terminal Pro-B–Type Natriuretic Peptide and Long-Term Mortality in Acute Coronary Syndromes

Torbjørn Omland, Anita Persson, Leong Ng, Russel O'Brien, Thomas Karlsson, Johan Herlitz, Marianne Hartford and Kenneth Caidahl

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N-Terminal Pro-B–Type Natriuretic Peptide and Long-Term Mortality in Acute Coronary Syndromes

Torbjørn Omland, MD, PhD, MPH; Anita Persson, MSc; Leong Ng, MD, PhD; Russel O'Brien, MD; Thomas Karlsson, MSc; Johan Herlitz, MD, PhD; Marianne Hartford, MD, PhD; Kenneth Caidahl, MD, PhD

Background—B-type natriuretic peptide (BNP) is a predictor of short- and medium-term prognosis across the spectrum of acute coronary syndromes (ACS). The N-terminal fragment of the BNP prohormone, N-BNP, may be an even stronger prognostic marker. We assessed the relation between subacute plasma N-BNP levels and long-term, all-cause mortality in a large, contemporary cohort of patients with ACS.

Methods and Results—Blood samples for N-BNP determination were obtained in the subacute phase in 204 patients with ST-elevation myocardial infarction (MI): 220 with non-ST segment elevation MI and 185 with unstable angina in the subacute phase. After a median follow-up of 51 months, 86 patients (14%) had died. Median N-BNP levels were significantly lower in long-term survivors than in patients dying (442 versus 1306 pmol/L; $P<0.0001$). The unadjusted risk ratio of patients with supramedian N-BNP levels was 3.9 (95% confidence interval, 2.4 to 6.5). In a multivariate Cox regression model, N-BNP (risk ratio 2.1 [95% confidence interval, 1.1 to 3.9]) added prognostic information above and beyond Killip class, patient age, and left ventricular ejection fraction. Adjustment for peak troponin T levels did not markedly alter the relation between N-BNP and mortality. In patients with no evidence of clinical heart failure, N-BNP remained a significant predictor of mortality after adjustment for age and ejection fraction (risk ratio, 2.4 [95% confidence interval, 1.1 to 5.4]).

Conclusions—N-BNP is a powerful indicator of long-term mortality in patients with ACS and provides prognostic information above and beyond conventional risk markers. **(*Circulation*. 2002;106:2913-2918.)**

Key Words: angina ■ myocardial infarction ■ natriuretic peptides ■ prognosis ■ risk factors

Acute coronary syndromes (ACS) encompass a continuum of cardiac ischemic events, ranging from unstable angina pectoris with no biochemical evidence of myocardial necrosis to ST-elevation acute myocardial infarction (AMI). The common denominator of ACS is a pathophysiologic process characterized by rupture of an atherosclerotic plaque, altered coronary vasomotor tone, platelet aggregation, and thrombosis.[1,2] The prognosis of patients with ACS varies widely, and clinical, electrocardiographic, and biochemical markers of adverse prognosis have been used to identify high-risk individuals in need of aggressive intervention. Recently, B-type natriuretic peptide (BNP) has been shown to provide valuable prognostic information in patients with ACS.[3–5] One previous study of 122 patients with predominantly ST-segment elevation AMI suggested that the N-terminal fragment of the BNP prohormone, N-BNP, may provide prognostic information superior to that obtained from BNP.[6] Sparse information exists regarding N-BNP in the setting of non–ST-segment elevation ACS. In one small-scale, cross-sectional study, N-BNP levels were higher in patients with unstable than in those with stable angina.[7] In a recent pilot study, N-BNP levels were predictive of short-term survival after adjustment for conventional contemporary risk markers, including troponin I.[8] The objective of the present study was to assess the long-term, prognostic value of N-BNP in an unselected, consecutive series of patients admitted to a Scandinavian teaching hospital with ACS. Because the presence of clinical heart failure during hospitalization after AMI is known to be associated with adverse prognosis as well as with high natriuretic peptide levels,[3,6,9] we were particularly interested in assessing the relation between N-BNP and all-cause mortality in patients with no signs of heart failure (ie, Killip class I) on admission and during the primary hospitalization, a group of patients commonly considered to be at low risk.

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Methods

Study Design and Patient Population

Patients with ACS, defined as a diagnosis of unstable angina pectoris or AMI, admitted to the coronary care unit of the Sahlgrenska

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From the Department of Cardiology, National Hospital (T.O.), Oslo, Norway; Departments of Cardiology (M.H., J.H., T.K.) and Clinical Physiology (A.P., K.C.), Sahlgrenska University Hospital, Göteborg, Sweden; and Department of Medicine and Therapeutics (R.O.B., L.N.), University of Leicester, Leicester, UK.

Correspondence to Kenneth Caidahl, MD, PhD, Department of Clinical Physiology, Sahlgrenska University Hospital, SE-41345 Göteborg, Sweden. E-mail caidahl@clinphys.gu.se

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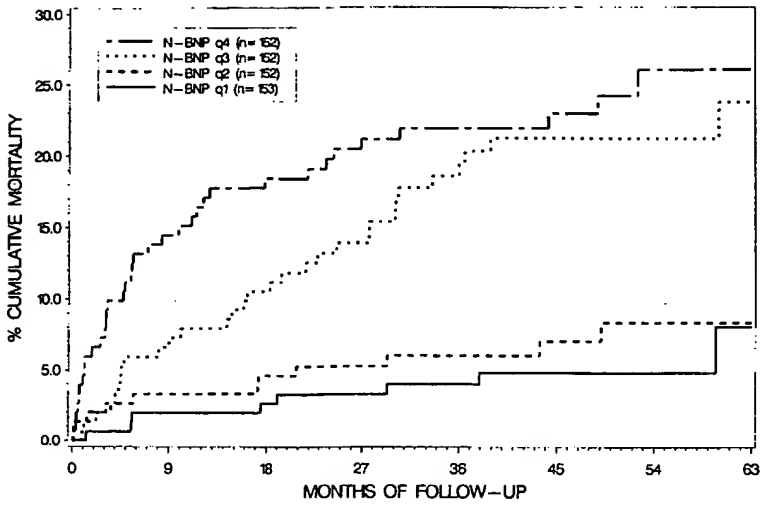

Figure 1. Kaplan-Meier survival curves for patients with acute coronary syndromes according to N-BNP quartile at baseline ($P<0.0001$ for difference between the two groups, q1+q2 vs q3+q4).

University Hospital, Gothenburg, Sweden from September 1995 to February 2000 were eligible for participation in an ongoing risk-stratification program. Patients who consented to blood sampling were included consecutively in the present study. The main exclusion criteria were age <18 or >80 years, noncoronary artery disease associated with a life expectancy <1 year, unwillingness or incapacity to provide informed consent, residence outside the city of Gothenburg, and prior admission resulting in inclusion in the study. The primary outcome measure of the study was all-cause mortality from the time of inclusion in the study to September 15, 2001. Survival status and date of death were obtained from the Death Registry of Western Sweden. The patients were prospectively classified according to maximum Killip class[10] on admission and during primary hospitalization. Electrocardiographic findings on admission were classified according to the presence of ST-segment elevation and ST-segment depression. Based on hospital records and personal interview, the patients were classified as having or not having a medical history of AMI, angina pectoris, congestive heart failure, diabetes mellitus, and arterial hypertension. The study protocol was approved by the Regional Ethics Committee before the initiation of the study. Informed consent was obtained from all participating patients.

Blood Sampling Procedures and Echocardiography

Peripheral blood samples for plasma N-BNP determination were obtained in the subacute phase (median 3 days) after hospital admission by direct venipuncture of an antecubital vein after the patient had been resting in the supine position for >30 minutes. Blood samples were immediately immersed in ice water and centrifuged within 1 hour, and EDTA plasma was aspirated. Plasma samples were stored at −70°C pending analysis. Echocardiographic investigation was performed by an experienced operator within 5 days of hospital admission. Biplane left ventricular ejection fraction (LVEF) was calculated by the disc sum method, and tracings were checked in motion mode for accuracy, as described previously.[11]

Assay of N-BNP

Our assay for N-BNP was based on the noncompetitive N-BNP assay described by Karl et al.[12] Peptides corresponding to the N-terminal (amino acids 1 to 12) and C-terminal (amino acids 65 to 76) of the human N-BNP were used to raise rabbit polyclonal antibodies.[13] IgG from the sera was purified on protein A sepharose columns. The C-terminal–directed antibody (0.5 μg in 100 μL for each well) was immobilized onto ELISA plates. The N-terminal antibody was affinity purified and biotinylated using biotin-X-N-hydroxysuccinimide ester (Calbiochem). Aliquots (20 μL) of samples or N-BNP standards were incubated in the C-terminal antibody coated wells with the biotinylated antibody for 24 hours at 4°C. ELISA plates were washed with 0.1% Tween in PBS, and streptavidin (Chemicon International Ltd) labeled with methyl-acridinium ester (5×10^6 relative light units/mL)[14] was added to each well. Plates were read on a Dynatech MLX Luminometer, with sequential injections of 100 μL of 0.1 mol/L nitric acid (with H_2O_2) and then 100 μL of NaOH (with cetyl ammonium bromide).[13] The lower limit of detection was 14.4 fmol/mL of unextracted plasma. Within and between assays, coefficients of variation were acceptable at 2.3% and 4.8%, respectively. There was no cross-reactivity with ANP, BNP, or CNP.

Statistical Analysis

Continuous data are presented as median and interquartile range. To test for differences between patients with supramedian versus inframedian N-BNP levels, the Mann-Whitney U and Fisher exact tests were used for ordered/continuous and categorical variables, as appropriate. For survival analysis, continuous and ordered variables were dichotomized using the 25th, 50th, or 75th percentile as the cut off. The cut-off value giving optimal discrimination with regard to all-cause mortality was selected for additional analysis. To visualize the relation between N-BNP levels and all-cause mortality, patients were subdivided according to the median value (545 pmol/L). Kaplan-Meier plots were generated, and the log rank test was used for comparison of the resulting survival curves. Cox proportional hazards regression was used to assess the prognostic value of N-BNP after adjustment for confounders, defined as the variables that separately decreased the risk ratio of supramedian N-BNP levels by at least 10%. The confounders identified were included simultaneously in 2 separate final models, one encompassing the complete patients sample with ejection fraction data and another comprising patients without clinical signs of heart failure (ie, Killip class I) on admission and during the index hospitalization. The optimal prognostic thresholds in the subgroups of patients with unstable angina, non–ST-segment elevation AMI, and ST-segment elevation AMI as index diagnosis were derived from receiver-operating characteristics plots. All probability values are two-tailed and were considered significant when <0.05. Risk ratios (RRs) are given with 95% confidence intervals.

Results

The study population consisted of 609 patients, 204 with ST-elevation AMI, 220 with non-ST segment elevation AMI, and 185 with unstable angina. Thrombolytic therapy or primary percutaneous coronary intervention was performed in 147 patients (24%), whereas rescue/planned percutaneous coronary intervention or coronary artery bypass grafting was performed in 153 patients (25%) during the primary hospitalization. The characteristics of the patients, subdivided according to the median level of plasma N-BNP, are listed in

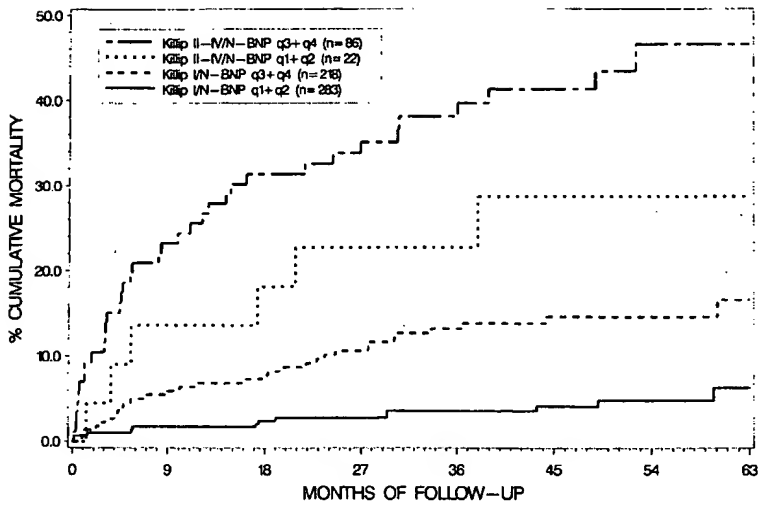

Figure 2. Kaplan-Meier survival curves for patients with acute coronary syndromes according to maximum Killip class during index hospitalization (I versus II through IV) and N-BNP levels below and above median (P=0.0001 for difference between N-BNP groups in maximum Killip class I patients and P=0.18 in maximum Killip class II through IV patients).

Table 1. The median N-BNP concentration in plasma was 545 pmol/L (interquartile range, 157 to 1435 pmol/L). As expected, the median plasma N-BNP concentrations differed according to the patients' index diagnosis (ST-segment elevation AMI, 1034 [390 to 2076] pmol/L; non-ST-segment elevation AMI, 644 [217 to 1507] pmol/L; unstable angina, 179 [62 to 477] pmol/L). Patients with supramedian N-BNP levels were significantly older and had higher serum creatinine, peak troponin T, and creatine kinase MB levels than those with inframedian N-BNP concentrations. Moreover, supramedian N-BNP values were associated with higher Killip class, lower LVEF, and a higher proportion of patients with ST-segment deviation, Q-wave changes, and anterior wall ECG changes.

N-BNP and All-Cause Mortality

No patient was lost to follow-up. After a median duration of follow-up of 51 months (range, 19 to 72 months), 86 patients (14%) had died. Ten deaths (2%) occurred during the first 30 days after hospital admission. Kaplan-Meier survival curves according to N-BNP quartile at baseline are presented in Figure 1. Median baseline N-BNP levels were significantly lower in long-term survivors than in patients dying (442 versus 1306 pmol/L; P<0.0001). The unadjusted RR of patients with supramedian N-BNP levels at baseline was 3.9 (95% confidence interval, 2.4 to 6.5) compared with those with inframedian values. No significant statistical interaction between index diagnosis and N-BNP regarding all-cause mortality was observed. The unadjusted RR of patients with supramedian N-BNP levels at baseline (ie, >545 pmol/L) compared with those with inframedian values was 4.7 (95% confidence interval, 1.4 to 15.6) in the subgroup with ST-segment elevation AMI, 5.6 (95% confidence interval, 2.2 to 14.5) in the subgroup with non–ST-segment elevation AMI, and 3.0 (95% confidence interval, 1.3 to 7.0) in the subgroup with unstable angina. Moreover, there was no significant interaction between thrombolytic therapy/primary percutaneous coronary intervention and N-BNP or between rescue/planned percutaneous coronary interventions/coronary artery bypass grafting and N-BNP with regard to all-cause mortality.

The association between potential confounders and long-term mortality is summarized in Table 2. Although several variables were univariate predictors of long-term mortality, only patient age, Killip class, and LVEF decreased the RR of N-BNP with >10%, suggesting that these factors were true confounders. Of note, although troponin T >25th percentile (ie, >0.05 μg/L) was related to mortality (RR 2.1 [95% confidence interval, 1.1 to 4.0]), the risk ratio of N-BNP was only slightly altered when adjusting for troponin T (unadjusted RR, 3.5 for supramedian N-BNP in patients with troponin T available, 3.3 after adjustment). The following potential confounder variables were tested in a series of 3-factor analyses but did not decrease the relative risk of N-BNP with more than the prespecified criterion for inclusion in the multivariate model (ie, 10%): patient sex (<1%), previous AMI (−2%), previous angina (3%), previous congestive heart failure (−4%), previous diabetes (1%), previous arterial hypertension (<1%), previous hyperlipidemia (−2%), current smoking (<1%), peak serum creatine kinase MB greater than lower quartile (7%), peak serum troponin T greater than lower quartile (−8%), serum creatinine greater than third quartile (−9%), ST-segment elevation on admission ECG (9%), ST-segment depression on admission ECG (−4%), T-wave changes on admission ECG (<1%), pathological Q-wave changes on admission ECG (−2%), anterior wall ST-segment deviation (3%), ST-segment elevation AMI as index diagnosis (5%), non–ST-segment elevation AMI as index diagnosis (−1%), and unstable angina as index diagnosis (4%).

In a multivariate model, adjusting for patient age, Killip class, and LVEF (ie, variables decreasing the RR of N-BNP with >10%), N-BNP remained significantly associated with mortality (Table 3). The adjusted RR of patients with supramedian N-BNP levels at baseline (ie, >545 pmol/L) compared with those with inframedian values was 2.6 (95% confidence interval, 0.7 to 8.9) in the subgroup with ST-segment elevation AMI, 2.3 (95% confidence interval, 0.8 to 6.6) in the subgroup with non–ST-segment elevation AMI, and 2.0 (95% confidence interval, 0.6 to 6.7) in the subgroup with unstable angina. The optimal prognostic thresholds in these 3 diagnostic subgroups, as assessed by receiver-operating characteristics analysis, was 1147 pmol/L in patients with ST-segment elevation AMI, 1284 pmol/L in

TABLE 1. Characteristics of Patients With N-BNP Levels Greater or Less Than the Median

Variable	N-BNP ≤545 pmol/L	N-BNP >545 pmol/L	P
Demographics			
Median age, y	62	69	<0.0001
Female sex, %	27	30	0.42
Previous medical history			
Myocardial infarction, %	23	28	0.14
Angina pectoris, %	55	46	0.04
Congestive heart failure, %	7	12	0.05
Diabetes mellitus, %	18	19	0.84
Arterial hypertension, %	40	43	0.41
Index diagnosis			<0.0001
ST-elevation myocardial infarction, %	20	45	
Non–ST-elevation myocardial infarction, %	33	39	
Unstable angina, %	47	16	
ECG findings			
ST-elevation, %	20	42	<0.0001
ST-depression, %	21	35	0.0002
Q-wave changes, %	5	21	<0.0001
Anterior wall location, %	20	42	<0.0001
Biochemical markers			
Median peak creatine kinase MB fraction, μg/L	14	78	<0.0001
Median peak troponin T, μg/L	0.1	1.9	<0.0001
Median creatinine, μmol/L	97	104	<0.0001
Clinical data			
Killip class II through IV on admission, %	4	11	0.0005
Maximum Killip class II through IV, %	7	28	<0.0001
Thrombolytic therapy/primary PCI, %	20	29	0.01
Rescue/planned PCI/CABG, %	31	19	0.001
Left ventricular function			
Median LVEF, %	60	50	<0.0001

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting.

patients with non–ST-segment elevation AMI, and 238 pmol/L in patients with unstable angina.

N-BNP and All-Cause Mortality in Killip Class I Patients

In the subgroup of patients with no clinical signs of heart failure on admission or during the primary hospitalization (n=501), 44 patients died during follow-up. The unadjusted RR for patients with supramedian N-BNP levels was 3.3 (95% confidence interval, 1.7 to 6.3) compared with those with inframedian values. In the subgroup of patients with LVEF measurements (n=403), the unadjusted RR for supramedian N-BNP was 3.7 (95% confidence interval, 1.8 to 7.9). In a multivariate model, adjusting for patient age and LVEF (ie, variables decreasing the RR for supramedian N-BNP >10%), N-BNP was still associated with long-term, all-cause mortality (risk ratio, 2.4 [95% confidence interval, 1.1 to 5.4]) (Table 3). Kaplan-Meier survival curves in patients stratified according to N-BNP levels and maximum Killip class during index hospitalization are presented in Figure 2.

Discussion

In a large, unselected, contemporary cohort of patients with ACS, we have demonstrated that N-BNP is a powerful indicator of long-term mortality. The relation seemed to be equally strong across the spectrum of ACS as well as in patients with and without evidence of clinical heart failure during the primary hospitalization.

N-BNP and Long-Term Mortality

Our results for N-BNP confirm and extend observations made in an important, recent, large-scale study of the prognostic value of BNP in patients with ACS.[5] In that study, which included patients from one of the treatment arms of the OPUS-TIMI 16 trial, BNP obtained during the first few days after the onset of ischemic symptoms was strongly and independently predictive of mortality at 1 and 10 months. In contrast to the OPUS-TIMI 16 BNP substudy, the present investigation was not a substudy of a multicenter, clinical drug trial but prospectively and primarily designed for evaluation of risk indicators in ACS. Although both studies included patients across the spectrum of ACS, from

TABLE 2. Prediction of All-Cause Mortality: Univariate Analyses

	Risk Ratio (95% Confidence Interval)	
Variable	All Patients	Max Killip Class I
N-BNP >545 pmol/L	3.9 (2.4 to 6.5)	3.3 (1.7 to 6.3)
Demographics		
Patient age >66 y	4.5 (2.7 to 7.5)	3.8 (2.0 to 7.3)
Female vs male sex	1.0 (0.6 to 1.6)	0.9 (0.5 to 1.9)
Previous medical history		
Myocardial infarction	2.0 (1.3 to 3.1)	1.6 (0.9 to 3.0)
Angina pectoris	1.2 (0.8 to 1.8)	1.1 (0.6 to 2.0)
Congestive heart failure	3.2 (1.9 to 5.3)	2.4 (1.0 to 5.6)
Diabetes mellitus	1.7 (1.1 to 2.8)	1.7 (0.8 to 3.3)
Arterial hypertension	1.0 (0.7 to 1.5)	1.1 (0.6 to 2.0)
ECG findings		
ST elevation	1.0 (0.6 to 1.5)	1.2 (0.6 to 2.2)
ST depression	1.7 (1.1 to 2.6)	1.8 (1.0 to 3.4)
Q-wave changes	1.6 (1.0 to 2.8)	1.4 (0.6 to 3.2)
Anterior wall location	1.2 (0.8 to 1.9)	1.3 (0.7 to 2.5)
Biochemical markers		
Peak creatine kinase MB >4 μg/L	1.4 (0.8 to 2.3)	0.9 (0.5 to 1.8)
Troponin T >0.5 μg/L	2.1 (1.1 to 4.0)	1.4 (0.6 to 3.1)
Creatinine >114 μmol/L	2.2 (1.4 to 3.4)	1.5 (0.7 to 2.8)
Clinical data		
Killip class on admission (II through IV vs I)	6.5 (4.0 to 10.4)	NA
Maximum Killip class (II through IV vs I)	5.6 (3.6 to 8.5)	NA
Left ventricular function		
LVEF <47%	3.4 (2.1 to 5.3)	3.8 (2.0 to 7.3)

q indicates quartile.

unstable angina to ST-segment elevation AMI, the mortality rate in the present study was significantly higher than in the OPUS-TIMI 16 BNP substudy, probably because of higher patient age and a higher proportion of patients with comorbidities. However, we believe that these features are common among contemporary patients with ACS, and our results are generalizable to other unselected patient groups.

TABLE 3. Multivariate Models

Variable	Risk Ratio (95% Confidence Interval)	*P*
All patients with ejection fraction measurements		
Patient age >66 y	2.5 (1.4 to 4.3)	0.001
LVEF <47%	1.9 (1.1 to 3.1)	0.01
Killip class on admission >1	3.2 (1.9 to 5.5)	<0.0001
N-BNP >545 pmol/L	2.1 (1.1 to 3.9)	0.02
Patients with ejection fraction measurements and maximum Killip class I on admission and during primary hospitalization		
Patient age >66 y	2.5 (1.2 to 5.0)	0.01
LVEF <47%	2.6 (1.3 to 5.2)	0.005
N-BNP >545 pmol/L	2.4 (1.1 to 5.4)	0.02

The observation that natriuretic peptides are powerful indicators not only of short-term and medium-term but also long-term prognosis across the spectrum of ACS is a novel one. We and others have previously shown that BNP[3] and N-BNP[6] are related to long-term prognosis in patients with predominantly ST-segment elevation AMI. However, no long-term follow-up data are yet available for patients with non–ST-segment elevation ACS. Moreover, none of the early, long-term studies made adjustments for modern, sensitive biochemical markers of myocardial necrosis. Importantly, as demonstrated both for BNP[5] and for N-BNP in the present investigation, these natriuretic peptides seem to provide complementary prognostic information to that obtained from troponin T.

Prognostic Value of N-BNP in Patients Without Clinical Heart Failure

Clinical heart failure is a poor prognostic sign in patients with ACS and is commonly regarded as a sign of significant ventricular dysfunction. LVEF is a frequently used index of left ventricular systolic function and a powerful prognostic indicator. Interestingly, LVEF and clinical classification of heart failure (ie, Killip classification) provide independent prognostic information, suggesting that factors other than systolic function are of importance for prognosis in these patients. Circulating natriuretic peptide levels are elevated both in patients with low ejection

fractions and in patients with clinical heart failure.[3,6,7] As previously shown for BNP,[5] we were able to demonstrate that N-BNP provides important prognostic information in ACS patients without clinical evidence of heart failure. Moreover, in this important subgroup, N-BNP added prognostic information to LVEF, a variable not adjusted for in the multivariate model of the OPUS-TIMI 16 BNP study.

Why Is N-BNP a Powerful Prognostic Indicator?

The pathophysiologic mechanisms responsible for the strong association between N-BNP and mortality cannot be deduced from the present study. However, our findings are compatible with the theory that BNP and N-BNP release, even in the absence of myocardial necrosis, is augmented by transient or permanent ventricular dysfunction induced by myocardial ischemia. Moreover, the magnitude of the increase in N-BNP may reflect the extent of the ischemic territory. In contrast to the highly sensitive and specific contemporary biochemical markers of myocardial necrosis, N-BNP (and BNP) elevation is associated with several other risk factors for adverse outcome, including advanced patient age, renal impairment, cardiac arrhythmias, and preexisting LV systolic or diastolic dysfunction. Consequently, BNP and N-BNP may in a unique way reflect a sum or integral of different risk markers. Indeed, the prognostic power of N-BNP may be directly related to this lack of specificity.

Does the Prognostic Value of BNP and N-BNP Differ?

BNP and N-BNP are released in a 1:1 fashion, but circulating concentrations may differ because of differing clearance characteristics. Although some early data suggested that the relative increase in circulating levels from the healthy state to heart failure is more pronounced for N-BNP than BNP[15] and the prognostic value in one early study tended to be slightly better for N-BNP than for BNP,[6] no well-powered study has so far compared the prognostic value in the setting of ACS. However, the OPUS-TIMI 16 BNP study results and data from the present investigation seem remarkably similar, suggesting that the difference, if any, is of limited practical consequence.

Limitations

A limitation of this and all similar studies is the fact that circulating concentrations of the natriuretic peptides before the ischemic event remain unknown. Accordingly, we cannot rule out the possibility that preexistent ventricular dysfunction, hypertrophy, or renal impairment, and not the ischemic injury per se, is the cause of N-BNP elevation and the relation to outcome. By adjusting for history of prior AMI, congestive heart failure, and hypertension, as well as for ejection fraction and serum creatinine, we attempted to minimize this effect. On a practical level, one could also argue that for risk stratification purposes, the main point is first to identify individuals at high risk, regardless of the cause. Assessment of the clinical utility of N-BNP may ultimately have to await clinical trials in which patients with high and low concentrations are randomized to different treatment strategies.

Conclusions

The present data strongly suggest that N-BNP levels in the first few days after the onset of symptoms are predictive of short- and long-term mortality in patients with ACS. Recently, a rapid, qualitative electrochemiluminescence immunoassay for automated determination of N-BNP has become commercially available, permitting the hospital clinician easy access to prognostic information not obtained from conventional risk markers. Whether N-BNP will find an important place in the diagnostic armamentarium of the clinical cardiologists will depend on future studies addressing the value of N-BNP measurements as a guide to different therapeutic strategies in patients with ACS.

Acknowledgments

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Acute Coronary Syndromes — Beyond Myocyte Necrosis

THE acute coronary syndromes, which comprise unstable angina, myocardial infarction without ST-segment elevation, and myocardial infarction with ST-segment elevation, continue to be a major health problem. Recent important advances in revascularization techniques, such as the advent of coronary-artery stenting, have been paralleled by developments in drug treatment. A typical approach to the acute coronary syndromes includes multiple treatment options: aspirin, beta-blockers, nitrates, unfractionated heparin, low-molecular-weight heparin, intravenous glycoprotein IIb/IIIa receptor inhibitors, clopidogrel, coronary stenting, thrombolytic agents, statins, and angiotensin-converting–enzyme (ACE) inhibitors. Therefore, one of the most important challenges in this era of cost containment is to identify the subgroup of patients who are at highest risk for adverse events in order to target the most aggressive interventional and pharmacologic therapies to these patients.

Use of the clinical characteristics of the patient, the electrocardiographic findings, and the levels of traditional serum markers of myocyte necrosis, such as the creatine kinase MB fraction and troponin I, is only partially successful in risk stratification. In patients who have unstable angina or myocardial infarction without ST-segment elevation, an elevated troponin level confers an increased short-term risk of death.[1] However, as compared with data from cohort studies, data from clinical trials reveal that the troponin level has less prognostic value.[1] One recent study demonstrated that the measurement of three markers of myocyte necrosis — troponin I, creatine kinase MB, and myoglobin — significantly increased physicians' ability to detect acute coronary syndromes, as compared with the use of each marker alone.[2] However, a patient who has unstable angina but no evidence of myocyte necrosis still has underlying rupture or erosion of plaques and may still have an increased risk of cardiac events.

As our understanding of the pathophysiology of the acute coronary syndromes advances, our ability to stratify patients according to risk improves in tandem. This issue of the *Journal* contains two articles — one by de Lemos et al.[3] and one by Bayes-Genis et al.[4] — on important new markers for use in risk stratification for acute coronary syndromes based on neurohormonal activation and inflammation. De Lemos and colleagues[3] measured plasma levels of brain (B-type) natriuretic peptide, a natriuretic and vasodilative peptide regulated by ventricular wall tension and stored mainly in the ventricular myocardium, in 2525 patients with acute coronary syndromes. A single measurement of B-type natriuretic peptide obtained a median of 40 hours after the onset of ischemic symptoms predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, or unstable angina, as well as the risk of new or progressive congestive heart failure and new or recurrent myocardial infarction. Moreover, the relation between the long-term risk of death and the B-type natriuretic peptide level was independent of electrocardiographic changes, troponin I levels, renal function, and the presence or absence of clinical evidence of congestive heart failure. Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

The observation that B-type natriuretic peptide, a marker of neurohormonal activation, is a prognostic factor in acute coronary syndromes is intriguing, given the importance of neurohormonal activation in acute myocardial infarction. Beta-blockers and ACE inhibitors, both of which counter neurohormonal activation, are crucial for the secondary prevention of myocardial infarction. Although both the sympathetic nervous system and the renin–angiotensin–aldosterone system are activated by acute myocardial infarction, ACE inhibition does not alter the circulating levels of B-type natriuretic peptide or norepinephrine.[5] Moreover, the B-type natriuretic peptide level is a potent predictor of the risk of death in pa-

tients with congestive heart failure, regardless of the cause. Indeed, in patients who have advanced left ventricular dysfunction treated with high-dose ACE inhibitors and beta-blockers, levels of B-type natriuretic peptide remain independently related to the risk of death and the progression of heart failure.[6]

In contrast to the long-standing knowledge that neurohormonal activation is deleterious in the acute coronary syndromes, the realization that inflammation has a critical role in the pathogenesis of these syndromes has occurred relatively recently. Inflammation contributes on several levels to the rupture of vulnerable atherosclerotic plaques or to the superficial intimal erosion, both of which may be followed by coronary thrombosis.[7] Many patients with acute myocardial infarction have multiple complex unstable plaques that are associated with adverse clinical outcomes, thereby suggesting that inflammation may have widespread effects throughout the coronary vasculature.[8]

A number of inflammatory serum markers acting independently of myocyte necrosis have been linked to both atherosclerosis and the acute coronary syndromes. Of these, the most widely studied inflammatory marker is C-reactive protein. Elevated levels of C-reactive protein are associated with an increased risk of recurrent events across the spectrum of acute coronary syndromes, independent of the presence or absence of myocyte necrosis.[9] More recently, C-reactive protein has been implicated as having direct atherothrombotic effects. C-reactive protein induces the production of tissue factor by monocytes,[10] facilitates the uptake of low-density lipoprotein by macrophages,[11] and directly induces the expression of vascular-cell adhesion molecules by human endothelial cells in the presence of serum.[12] In addition, C-reactive protein induces the expression of monocyte chemoattractant protein 1 by human endothelial cells, an inflammatory effect that can be inhibited by a statin as well as by a protein complex that induces the expression of peroxisome-proliferator–activated receptor α.[13]

Bayes-Genis and colleagues present histologic evidence that pregnancy-associated plasma protein A (PAPP-A), a metalloproteinase and an activator of proatherogenic insulin-like growth factor I (that was first identified in pregnant women), is expressed in ruptured and eroded plaques but not stable plaques.[4] Circulating PAPP-A levels were significantly elevated in patients with acute coronary syndromes. Elevated PAPP-A levels appeared to identify patients with unstable angina in the absence of elevations in either troponin I or C-reactive protein. Therefore, this inflammatory marker may have the ability to detect at-risk patients with rupture or erosion of plaques before and independent of the advent of myocyte necrosis.

Although it has not been determined whether PAPP-A can degrade extracellular matrix,[4] it is noteworthy that PAPP-A is a metalloproteinase. The production of matrix metalloproteinases by macrophage foam cells is thought to contribute to the rupture of plaques in patients with acute coronary syndromes by weakening the fibrous cap of vulnerable plaques.[7] Statins, which are critical treatments in acute myocardial infarction for both primary and secondary prevention, have a number of antiinflammatory effects. Statins reduce C-reactive protein levels[14] as well as stabilize atherosclerotic plaque by decreasing lipid content, lipid oxidation, inflammation, matrix metalloproteinase 2 immunoreactivity, and apoptosis, while increasing the collagen content of plaques and the levels of tissue inhibitor of metalloproteinase 1.[15]

Taken together, the articles by de Lemos et al. and Bayes-Genis et al. highlight the continued importance of elucidating the mechanisms underlying the acute coronary syndromes. At the very least, tests for both neurohormonal activation, reflected by an elevation in B-type natriuretic peptide, and inflammation, reflected by the release of PAPP-A, may augment our ability to identify patients with acute coronary syndromes who are at risk for adverse events. The use of these markers could thus potentially augment our ability to reserve the most expensive and aggressive therapies for patients who have the highest risk. Finally, these insights may also stimulate the development of drugs, such as antiinflammatory and antineurohormonal agents, that will further improve the outcomes of patients with acute coronary syndromes.

LeRoy E. Rabbani, M.D.
Columbia University College of Physicians and Surgeons
New York, NY 10032

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Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction

A M Richards, M G Nicholls, T G Yandle, H Ikram, E A Espiner, J G Turner, R C Buttimore, J G Lainchbury, J M Elliott, C Frampton, I G Crozier and D W Smyth

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Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction

A M Richards, M G Nicholls, T G Yandle, H Ikram, E A Espiner, J G Turner, R C Buttimore, J G Lainchbury, J M Elliott, C Frampton, I G Crozier, D W Smyth
(The Christchurch Cardioendocrine Research Group)

Abstract

***Objective*—To determine the relations of plasma levels of brain natriuretic peptide (BNP), atrial natriuretic factor (ANF), N-terminal ANF (N-ANF), cyclic guanosine monophosphate (cGMP; the cardiac peptide second messenger), and plasma catecholamines to left ventricular function and to prognosis in patients admitted with acute myocardial infarction.**

***Design*—Plasma hormones and ventricular function (radionuclide ventriculography) were measured 1–4 days after myocardial infarction in 220 patients admitted to a single coronary care unit. Radionuclide scanning was repeated 3–5 months after infarction. Clinical events were recorded over a mean period of 14 months.**

***Results*—Both early and late left ventricular ejection fraction (LVEF) were most closely related to plasma BNP ($r = -0.60$, $n = 220$, $p < 0.001$; and $r = -0.53$, $n = 192$, $p < 0.001$, respectively), followed by ANF, N-ANF, cGMP, and the plasma catecholamines. Early plasma BNP concentrations less than twofold the upper limit of normal (20 pmol/l) had 100% negative predictive value for LVEF < 40% at 3–5 months after infarction. In multivariate analysis incorporating all the neurohormonal factors, only BNP remained independently predictive of LVEF < 40% ($p < 0.005$). Survival analysis by median levels of candidate predictors identified BNP as the most powerful discriminator for death ($p < 0.0001$). No early deaths (within 4 months) occurred in patients with plasma BNP concentrations below the group median (27 pmol/l), and over follow up only three of 26 deaths occurred in this subgroup. Of all episodes of left ventricular failure, 85% occurred in patients with plasma BNP above the median ($p < 0.001$). In multivariate analyses, BNP alone gave additional predictive information beyond sex, age, clinical history, LVEF, and plasma noradrenaline for both subsequent onset of LVF and death.**

***Conclusions*—Plasma BNP measured within 1–4 days of acute myocardial infarction is a powerful independent predictor of left ventricular function, heart failure, or death over the subsequent 14 months, and superior to ANF, N-ANF, cGMP, and plasma catecholamines.**

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Department of Cardiology, Christchurch Hospital, PO Box 4345, Christchurch, New Zealand
A M Richards
H Ikram
J G Lainchbury
J M Elliott
I G Crozier
D W Smyth

Department of Endocrinology, Christchurch Hospital
T G Yandle
E A Espiner

Department of Nuclear Medicine, Christchurch Hospital
J G Turner

Department of Medicine, Christchurch School of Medicine, Riccarton Avenue, Christchurch, New Zealand
M G Nicholls
R C Buttimore
C Frampton

Correspondence to:
Professor Richards.
email: bgriffin@chmeds.ac.nz

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Various circulating factors reflect left ventricular function and predict cardiovascular prognosis in a spectrum of cardiovascular disease ranging from severe heart failure of varied aetiology to well defined asymptomatic ischaemic left ventricular impairment.[1-14] In recent reports the cardiac peptides have received particularly close attention as cardiovascular markers.[5-11 13-17] However, which of atrial natriuretic factor (ANF), N-terminal ANF (N-ANF), or brain natriuretic peptide (BNP) is the most useful, whether plasma concentrations of the cardiac peptide second messenger cyclic guanosine monophosphate (cGMP) are as useful, and whether the cardiac peptides (or cGMP) are superior to other neurohumoral factors or add information beyond clinical indicators and left ventricular imaging remain unexplored or disputed.[10-13 16 17]

To test the hypothesis that BNP, which is a ventricular product released in response to chamber wall stress, would prove superior to other markers, a prospective study was conducted to provide the first report of concurrent measurements and comparisons of plasma BNP, ANF, N-ANF, c-GMP, noradrenaline, and adrenaline in detecting left ventricular dysfunction (assessed by radionuclide ventriculography) and predicting clinical events after myocardial infarction.

Methods

We studied 220 patients (table 1) admitted to the Christchurch Hospital coronary care unit with acute myocardial infarction between November 1994 and December 1995. Acute myocardial infarction was defined by the presence of typical cardiac ischaemic symptoms, ischaemic change on the ECG in two or more contiguous leads, and peak elevation of plasma creatine kinase to at least twice normal (400 U/l). Inclusion criteria included age less than 80 years, absence of cardiogenic shock, and survival for at least 24 hours after myocardial infarction.

Blood samples were taken 24 to 96 hours after the onset of symptoms, in the morning (07:00–13:00), from an indwelling intravenous cannula placed at least 30 minutes before sampling and with the patient resting quietly while semirecumbent. Samples were taken into chilled EDTA vacutainers, placed immediately on ice, centrifuged within 20 minutes at 4°C,

Table 1 Clinical, neurohormonal, and left ventricular scan data from 220 acute myocardial infarction patients

Clinical variables	
Age (years)	63 (10)
Male sex (%)	78
Body mass index (kg/m²)	27.0 (4.6)
Position of infarct (%)	
Anterior	39
Inferior	51
Other	10
Peak creatine kinase (U/l) (< 150)*	1971 (1506)
Peak troponin T (U/l) (< 0.01)*	13 (8)
Total cholesterol (mmol/l)	6.13 (1.3)
Previous history (%)	
Angina	45
Myocardial infarction	24
Cerebrovascular disease	11
Peripheral vascular disease	10
Diabetes mellitus	14
Hypertension	39
Smoker, current	26
Smoker, past	36
Hormone and scan data	
Brain natriuretic peptide (pmol/l)	32 (21)
Atrial natriuretic factor (pmol/l)	38 (32)
N-terminal atrial natriuretic factor (pmol/l)	2299 (1776)
Cyclic guanosine monophosphate (nmol/l)	6.3 (3.3)
Noradrenaline (nmol/l)	2.22 (1.40)
Adrenaline (pmol/l)	210 (184)
Left ventricular ejection fraction (%)	46 (13)
Left ventricular end diastolic volume (ml)	154 (53)
Left ventricular end systolic volume (ml)	87 (47)

Values are mean (SD).
*Normal values.

and the plasma stored at −80°C before assay. Cardiac peptides were measured by our locally developed radioimmunoassays,[18 19] cGMP by the method of Steiner *et al*,[20] and catecholamines by high performance liquid chromatography with electrochemical detection.[21] Intra-assay and interassay coefficients of variation were within 8% and 9%, respectively, for all assays.

Left ventricular function was assessed by radionuclide ventriculography within 24 hours of blood sampling. Each study was performed using a General Electric 400AC gamma camera interfaced to a General Electric 3000i computer system (General Electric Medical Systems, Milwaukee, Wisconsin, USA) following standard in vivo technetium-99m red blood cell labelling. Patients underwent repeat radionuclide scanning at three to five months after infarction.

Clinical events including death, acute ischaemic coronary syndromes, and heart failure (defined by presence of new symptoms of dyspnoea and/or oedema, with one or more concordant signs including ventricular gallop rhythm, pulmonary crepitations, raised venous pressure, and radiological evidence of left ventricular failure) were recorded over a mean follow up period of 14 months.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). The Pearson product moment correlation coefficient was used to measure linear correlations between variables. For correlation analysis the log of neurohumoral factors was used to normalise the distribution of data. Correlations were compared using a z test on normally transformed correlation coefficients.

The relative abilities of neurohumoral factors to predict left ventricular ejection fraction (LVEF) < 40%, or new onset heart failure during follow up were assessed by receiver operating characteristic (ROC) analysis. Areas under the ROC curves for each marker were compared using the method of Hanley and McNeil.[22] Optimal values for specificity and sensitivity were estimated by finding the position on the ROC curves with the minimum Euclidean distance to the point of perfect specificity and sensitivity (100%, 100%). Multiple logistic regression was undertaken to test for independent prediction of LVEF < 40% by one or more neurohumoral factors.

Mean levels of neurohumoral factors, ejection fraction, and ventricular volumes were compared using independent *t* tests for patients experiencing or spared specific adverse events. Cumulative adverse event rates were compared using χ^2 tests (with Yates' correction for low expected frequencies) and risk ratios (with 95% confidence intervals) calculated between patient groups with admission levels above and below the median of individual neurohumoral factors, ejection fraction, and left ventricular volumes. Kaplan–Meier survival curves were constructed for subgroups with neurohormonal and ventricular scan variables above and below the group medians.

Multivariate analyses were conducted including demographic and clinical variables (age, sex, history of previous myocardial infarction, hypertension, diabetes, and previous heart failure) as standard predictors forced into the model to test for any further independent predictive power provided by candidate indicators (including LVEF and plasma neurohormones) for three specific outcomes—left ventricular failure, death, and the combined end point of left ventricular failure and/or death. Concordant with χ^2 analyses of event rates and Kaplan–Meier analyses, candidate markers were entered in the multiple logistic regression analyses as binary variables (above or below the median).

Results

Between November 1994 and December 1995, 451 patients with myocardial infarction were admitted to the coronary care unit. Four per cent died within 24 hours of onset of symptoms, 11% were excluded as peak creatine kinase did not exceed 400 U/l, and a further 10% were aged over 80 years or suffered cardiogenic shock. Of the remaining 338 eligible patients, 220 consented to participate in the study. Clinical and demographic features of the group are given in table 1. At discharge 96% of the group were receiving aspirin, 84% β blockers, 47% angiotensin converting enzyme (ACE) inhibitors, and 24% diuretics. Plasma neurohumoral results and left ventricular indices for the group are given in table 1. Mean plasma concentrations of both ANF and BNP were raised ($p < 0.001$) to well above the upper limit of normal (2 SD above mean of 168 age matched normal subjects = 25 pmol/l and 10 pmol/l for ANF and BNP, respectively) and showed a broad dispersion. In contrast, mean noradrenaline and adrenaline concentrations were within the normal range (< 3.9 nmol/l and < 500 pmol/l, respectively). Normal ranges

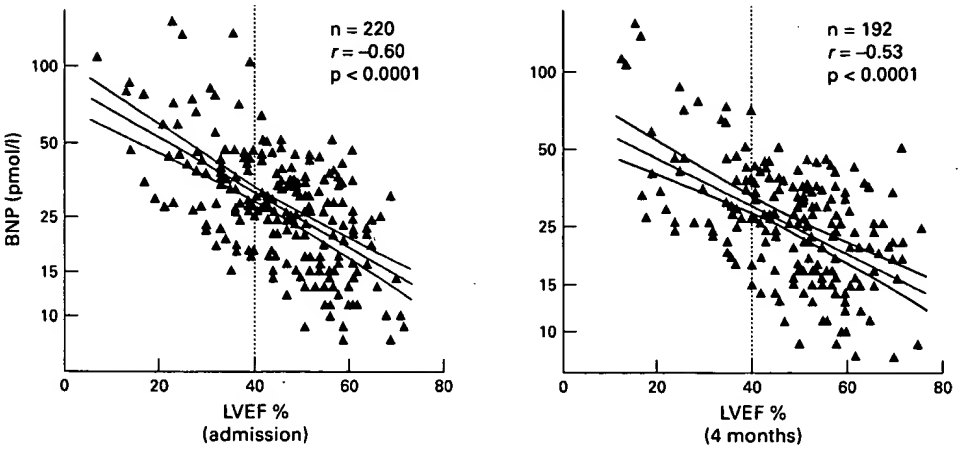

Figure 1 Individual early postinfarction plasma concentrations of brain natriuretic peptide (BNP; log scale) plotted against corresponding early (left; "admission") and late (right; "4 months") postinfarction radionuclide scan left ventricular ejection fraction (LVEF) (regression lines with 95% confidence intervals) for 220 patients with myocardial infarction. Vertical dashed lines are marked at 40% ejection fraction. BNP concentrations < 20 pmol/l (that is, less than twice the upper limit of normal) correspond to a late ejection fraction greater than 40%.

for plasma cGMP and N-ANF have yet to be formally established but the concentrations were significantly higher than measured in 35 normal subjects (not age matched).

Strong positive relations were observed between early plasma ANF and concurrent levels of BNP, cGMP, and N-ANF ($r = 0.74$, 0.69, and 0.60, respectively; n = 220; all $p < 0.001$) but associations of any cardiac peptide (or cGMP) with noradrenaline were weaker ($r = 0.07$–0.31; p = NS–<0.001).

HORMONES AND LEFT VENTRICULAR EJECTION FRACTION

Inverse relations between LVEF and concomitant cardiac peptide concentrations were strongest for BNP ($r = -0.60$, n = 220, $p < 0.0001$) and weaker for ANF (−0.47; $p < 0.001$), N-ANF (−0.31; $p < 0.001$), and cGMP (−0.42; $p < 0.001$). Relations of LVEF with noradrenaline and adrenaline ($r = -0.26$ and −0.17), though statistically significant ($p < 0.001$ and $p < 0.05$ respectively), were weak. The association between BNP and LVEF was significantly stronger than for any other marker ($p < 0.05$–0.001) except ANF ($p = 0.063$). The slope and strength of the relations between BNP and LVEF were similar whether BNP values were plotted against early or late LVEF measurements (fig 1).

ROC analyses of the sensitivity and specificity of neurohormonal markers to detect an LVEF value of < 40% (table 2) showed that the optimum level of plasma BNP (≥ 25 pmol/l) had greater sensitivity (81%) than any other marker, and comparison of ROC curves indicated a statistically significant advantage for BNP over noradrenaline and adrenaline ($p < 0.05$ for both). Multiple logistic regression analysis suggested that BNP alone predicted an LVEF of < 40% independently of all the other neurohumoral factors measured ($p < 0.005$). Plasma BNP concentrations below 20 pmol/l measured one to four days postinfarction gave 100% predictive power that LVEF measured three to five months later would be not less than 40% (fig 1). In contrast, the positive predictive power of all hormones was modest (only 32–47% for LVEF < 40%). BNP concentrations between 25 and 60 pmol/l corresponded to LVEF values over a wide range (20–70%; fig 1). Only in the small group of patients with early postinfarct BNP concentrations over 60 pmol/l (n = 15/220) was there

Table 2 Sensitivity, specificity, and predictive power of optimal levels of markers for left ventricular ejection fraction (LVEF) < 40% and for subsequent development of left ventricular failure (LVF)

	Optimum level	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
LVEF <40%					
BNP (pmol/l)	≥25	**81**	56	48	85
ANF (pmol/l)	≥33	64	63	47	77
N-ANF (pmol/l)	≥1620	66	43	37	71
cGMP (nmol/l)	≥5.89	65	62	47	78
Noradrenaline (nmol/l)	≥1.81	63	55	42	74
Adrenaline (pmol/l)	≥144	71	50	32	65
LVF					
BNP (pmol/l)	≥33	**84**	**77**	**47**	**95**
ANF (pmol/l)	≥37	81	75	46	94
N-ANF (pmol/l)	≥2200	**84**	**69**	**42**	**94**
cGMP (nmol/l)	≥6.31	72	70	39	90
Noradrenaline (nmol/l)	≥1.85	72	59	36	87
Adrenaline (pmol/l)	≥156	71	56	34	86
LVEF (%)	≤47	79	58	33	91

Highest values for each end point are given in bold type. Optimum levels of candidate indicators were selected from receiver operating characteristic curves (fig 3).
ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; LVEF, left ventricular ejection fraction; N-ANF, N-terminus ANF; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Plasma neurohormone concentrations and left ventricular indices measured one to four days after myocardial infarction in patients with and without subsequent adverse events over a mean 14 month follow up

	n	BNP (pmol/l)	ANF (pmol/l)	N-ANF (pmol/l)	cGMP (nmol/l)	Adrenaline (pmol/l)	Noradrenaline (nmol/l)	LVEF (%)	LVEDV (ml)	LVESV (ml)
Death										
Yes	26	52 (35)***	68 (66)***	4054 (2333)***	8.5 (5.8)***	210 (112)	2.84 (1.79)*	35 (16)***	203 (86)***	140 (73)***
No	194	29 (17)	34 (22)	2064 (1346)	6.0 (2.6)	204 (174)	2.19 (1.19)	47 (12)	147 (38)	79 (32)
Heart failure										
Yes	56	50 (30)***	65 (51)***	3640 (2113)***	8.8 (4.6)***	256 (160)*	3.20 (1.68)***	36 (15)***	183 (69)***	122 (59)***
No	164	25 (12)	29 (14)	1841 (1074)	5.5 (2.0)	188 (169)	1.95 (0.96)	49 (10)	144 (35)	75 (27)
Acute coronary syndrome										
Yes	66	34 (23)	40 (41)	2448 (1618)	6.5 (3.6)	174 (116)	2.26 (1.15)	46 (15)	149 (49)	84 (44)
No	154	31 (20)	37 (28)	2236 (1848)	6.3 (3.2)	218 (194)	2.27 (1.39)	46 (13)	156 (55)	88 (48)

Values are mean (SD).
*p < 0.05; ***p < 0.001, comparison of those with and without event.
ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NA, noradrenaline; N-ANF, N-terminus ANF.

100% positive predictive power for an LVEF of < 40% (fig 1).

HORMONES AND CLINICAL EVENTS

During follow up, 26 deaths (23 cardiovascular), 56 heart failure events, and 65 acute coronary syndrome events were recorded (cumulative event rates of 12%, 25%, and 30%, respectively). Early postinfarct values for BNP, ANF, N-ANF, cGMP, noradrenaline, and left ventricular volume were significantly higher and LVEF was significantly lower in patients who died or developed heart failure in the follow up period (table 3). Adrenaline concentrations were higher in those developing heart failure but not significantly so in patients who died. Neither neurohormones nor LVEF differed between those incurring or avoiding new acute coronary ischaemic syndromes.

ROC analysis indicated that early neurohumoral levels had generally better sensitivity and specificity for predicting the subsequent development of left ventricular failure than for indicating an LVEF value of < 40% (table 2). Optimal postinfarct values for BNP, ANF, and N-ANF had sensitivities of 80–84% and specificities of 77%, 75%, and 69%, respectively, for prediction of left ventricular failure. Other markers had lesser specificity and sensitivity.

Median early BNP and ANF values in particular discriminated between patients destined or not to die or to develop heart failure (table 4). No patient with early postinfarct BNP concentrations below the group median died in the first four months after infarction (fig 2). Over 80% of those developing heart failure over follow up had early BNP or ANF concentrations above the group median. N-ANF and cGMP values and left ventricular scan indices had comparable though marginally weaker predictive power for heart failure, while noradrenaline and adrenaline were clearly much weaker (tables 2–4). Kaplan–Meier survival curves for subgroups divided according to median hormone values and left ventricular scan data (fig 2) showed significant separation of curves for BNP, N-ANF, ANF (fig 2), left ventricular end systolic volume, left ventricular end diastolic volume, and LVEF ($p < 0.001$ for all three left ventricular scan indices), but not for cGMP (fig 2), adrenaline ($p = 0.91$), or noradrenaline ($p = 0.76$).

Multiple logistic regression indicated that both BNP ($p < 0.05$) and age ($p < 0.05$) were predictive of death independently of sex, clinical history, noradrenaline, and LVEF. BNP ($p < 0.01$), age ($p < 0.05$), a previous history of heart failure ($p < 0.05$), and LVEF ($p < 0.05$) all gave independent information predictive of left ventricular failure. Similarly, for the composite end point of death and/or heart failure, BNP ($p < 0.001$), LVEF ($p < 0.05$), and age ($p < 0.05$) all gave independent information. When serial analyses were conducted substituting ANF, N-ANF, and then cGMP (in place of BNP), all three failed to give independent prediction of death though all achieved statistical significance for independent prediction of left ventricular failure or the composite end point of death and/or left ventricular failure.

Table 4 Risk ratios (95% confidence intervals) for adverse events according to median levels of neurohormonal markers and left ventricular scan indices measured one to four days after myocardial infarction (n = 220)

	Median value	Relative risk (95% confidence interval)		
		Death (n = 26)	Heart failure (n = 56)	Unstable coronary syndrome (n = 65)
BNP (pmol/l)	27	6.0 (2.1 to 16.9)***	5.0 (2.7 to 9.5)***	1.4 (1.0 to 2.2)
ANF (pmol/l)	30	2.8 (1.2 to 6.4)**	5.4 (2.8 to 10.5)***	1.1 (0.7 to 1.6)
N-ANF (pmol/l)	1865	4.2 (1.6 to 10.7)***	3.3 (1.9 to 5.8)***	1.2 (0.8 to 1.9)
cGMP (nmol/l)	5.7	1.3 (0.6 to 2.8)	3.3 (1.9 to 5.8)***	1.1 (0.8 to 1.7)
Noradrenaline (nmol/l)	1.94	0.9 (0.4 to 1.8)	1.9 (1.2 to 3.1)**	1.1 (0.7 to 1.7)
Adrenaline (pmol/l)	164	1.0 (0.5 to 2.1)	1.8 (1.1 to 2.9)*	0.8 (0.5 to 1.2)
LVEF (%)	47	2.6 (1.1 to 5.9)*	3.4 (1.9 to 6.1)***	1.1 (0.7 to 1.7)
LVEDV (ml)	145	2.6 (1.1 to 5.9)*	2.1 (1.3 to 3.4)**	0.9 (0.6 to 1.4)
LVESV (ml)	77	3.5 (1.4 to 8.3)**	4.1 (2.3 to 7.6)***	1.0 (0.7 to 1.5)

*p < 0.05; **p < 0.01; ***p < 0.001 (χ^2 analysis).
For neurohormonal markers and left ventricular volumes, risk ratios were calculated from event rates above divided by rates below group medians, and for LVEF below/above the median.
ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; N-ANF, N-terminus ANF.

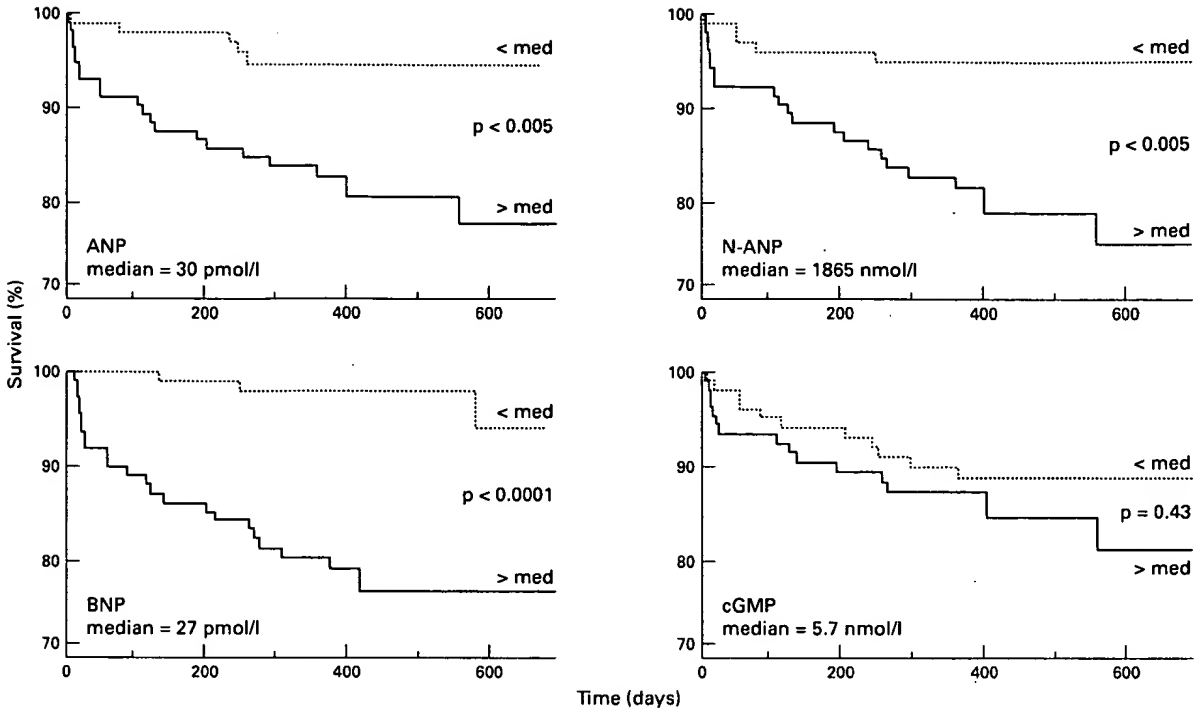

Figure 2 Kaplan–Meier survival curves for subgroups with early postinfarction plasma peptides (ANF, N-ANF, BNP) and cGMP concentrations above (solid line) and below (dashed line) the group median in 220 patients with myocardial infarction. ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; N-ANF, N-terminal ANF.

Discussion

Recent reports indicate that neurohormonal measurements reflect left ventricular function and add useful information beyond clinical features and cardiac imaging procedures in predicting outcomes after myocardial infarction, and in both staging and prognosis for patients with established congestive heart failure.[23 24] However, there is conflict and inconsistency in existing reports.[2 5 10-13]

Our study provides the first prospective single centre comparison of the value of multiple neurohumoral measurements in assessing left ventricular function and prognosis in a typical and substantial population of patients suffering myocardial infarction and passing through a single coronary care unit within little over a year. The study design also allowed us to examine the relative ability of early measurements of an array of neurohormonal variables to predict left ventricular function several months after infarction. It is also the first report to extend the investigation of an array of neurohormonal variables to their potential predictive power for morbid postinfarction end points (heart failure and ischaemic syndromes) as well as mortality. Whereas in many previous studies subjects have been preselected according to left ventricular function or symptomatic status,[2 7 12 15 25] in our investigation we tested the applicability of neurohormonal measurements in a substantial population embracing a wide spectrum of pre-existing morbidity, age, and severity of infarction as typifies current coronary care practice in the thrombolytic era. The protocol was practical, requiring a single sample for blood hormone levels and initial radionuclide scanning within a 24 to 96 hour window following the onset of infarction.

HORMONES AND LEFT VENTRICULAR EJECTION FRACTION

The plasma concentrations of the cardiac peptides, and BNP in particular, were strongly related to left ventricular ejection fraction measured both early (one to four days) and late (three to five months) after infarction. These results concur with those reported by Davidson *et al*, Yamamoto *et al*, and Motwani *et al*,[10 11 17] and contrast with those of Omland *et al*,[13] in showing that the inverse correlation of BNP and LVEF is stronger than those for ANF or N-ANF. This relation has practical value in that a plasma BNP of less than twice the upper limit of normal within days of myocardial infarction carried 100% predictive power that late LVEF would not fall below 40%. However, the positive predictive power of these hormone levels for impaired left ventricular function is limited. In contrast to data from Motwani *et al*,[17] BNP levels from 20 to 60 pmol/l were associated with a broad range of LVEF values, from normal to severely reduced (20% to 70%).

HORMONES AND CLINICAL EVENTS

BNP had the highest sensitivity, specificity, positive predictive value, and negative predictive value (table 2) for heart failure during follow up. Multivariate analyses indicated that any one of BNP, ANF, N-ANF, or cGMP added additional information beyond clinical features, noradrenaline concentrations, and LVEF in predicting heart failure or the composite end point of death and/or heart failure. Among the

cardiac peptides, BNP and ANF were the most powerful in this regard, with nothing to be gained from measuring more than one of these, or N-ANF or cGMP. LVEF also provided independent information.

BNP was also the strongest single hormonal predictor of death by several univariate analyses (tables 3 and 4; fig 1). Multivariate analyses also indicated that BNP alone among the hormones tested was independently predictive of death. For left ventricular failure or the composite end point of death and/or left ventricular failure, any one of ANF, N-ANF, cGMP, and BNP provided independent predictive information (as did age and LVEF). BNP has previously been reported to predict mortality in some categories of cardiac injury.[13 14 16 17] In contrast to smaller series in which BNP has been reported to correlate less well with LVEF but better with mortality[13] or better with mortality but less well with heart failure[17] than ANF, our larger study shows that BNP is consistently more closely related to left ventricular dysfunction and mortality than the other neurohormones measured, while retaining an association with left ventricular failure comparable to that seen with the other cardiac peptides and with left ventricular scan data.

Although mean noradrenaline concentrations were increased in those dying or developing left ventricular failure during follow up, in multivariate analysis noradrenaline did not provide independent information. Generally, our findings are in accord with reports that have shown the superiority of ANF over noradrenaline as a cardiovascular marker[5 15 25] in the postinfarction setting, and our data extend this conclusion to BNP, N-ANF, and cGMP.

Although plasma cGMP maintained obvious relations with concomitant plasma cardiac peptides (most notably ANF), it was clearly a less powerful indicator of LVEF or of death than BNP. This is presumably because plasma cGMP concentrations merely reflect spillover into the circulation of a tiny proportion of the cGMP produced intracellularly. Changes in cGMP also occur in response to various other stimuli including nitric oxide, as well as cardiac peptide levels. However, it performed as well as N-ANF and better than noradrenaline in the prediction of heart failure.

It has previously been reported that N-ANF predicts prognosis and left ventricular function.[6-10] In the current study, N-ANF was consistently and significantly related to the other cardiac peptides and to cGMP as well as to LVEF and to adverse outcomes. Notably N-ANF had a high sensitivity for predicting heart failure (table 2). However, it clearly performed less well than BNP (or ANF) as a predictor of death or as an indicator of LVEF. The latter seems intuitively acceptable as BNP is released from the ventricle (the only truly "ventricular" hormone measured in the study) in response to left ventricular wall stress and might logically be most closely related to the state of the left ventricle. The finding conflicts with other studies[10 13] reporting that N-ANF is equal or superior to BNP in predicting an LVEF $\leq$ 45% in smaller groups with left ventricular impairment of mixed aetiology.[10] The current study indicates that within days or months of myocardial infarction, N-ANF will be less closely related to left ventricular size and function than BNP.

Non-fatal acute coronary syndromes were not predicted by any of the candidate markers measured, perhaps reflecting the weakness of any relation between intracardiac pressures (the prime regulator of cardiac peptide release) and vulnerability to coronary atherosclerotic plaque rupture.

LIMITATIONS

A shortcoming of our study, and all similar studies, is the necessary limit to the number of potential neurohumoral markers assessed. Renin was not measured because many of the group received converting enzyme inhibitors, thus distorting any relation between renin and ventricular function or cardiovascular prognosis. Endothelin has shown promise despite its diffuse vascular (rather than specific cardiac) origin, and warrants further study.[26-28] Similarly, further consideration of cytokines including tumour necrosis factor is also required.[29 30] The list of circulating factors with potential prognostic value will inevitably expand with time.

CONCLUSIONS

Among plasma cardiac peptides, cGMP, and the catecholamines, the ventricular hormone BNP best reflects left ventricular function and gives independent prognostic information on the risk of death or heart failure in the months following myocardial infarction. Stratification of patients into low and high risk groups can be greatly facilitated by plasma BNP measurements and these could reasonably be included in the routine clinical work up of patients following myocardial infarction.

We gratefully acknowledge the assistance of Ms Leanne Liggett and Mrs Rose Richards (research assistants), nuclear medicine and endocrine department technical and nursing staff, and coronary care nursing staff. Funding was provided by grants from the National Heart Foundation of New Zealand and the Health Research Council of New Zealand. Secretarial assistance was provided by Barbara Griffin. AMR holds the National Heart Foundation (NZ) Chair of Cardiovascular Studies.

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☐ **1:** Circulation 2002 Apr 16;105(15):1760-3

Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide.

Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E.

TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, Mass 02115, USA. msabatine@partners.org

BACKGROUND: In patients with acute coronary syndromes (ACS), troponin I (TnI), C-reactive protein (CRP), and B-type natriuretic peptide (BNP) each predict adverse cardiac events. Little is known, however, about the utility of these biomarkers in combination. METHODS AND RESULTS: Baseline measurements of TnI, CRP, and BNP were performed in 450 patients in OPUS-TIMI 16. Elevations in TnI, CRP, and BNP each were independent predictors of the composite of death, myocardial infarction (MI), or congestive heart failure (CHF). When patients were categorized on the basis of the number of elevated biomarkers at presentation, there was a near doubling of the mortality risk for each additional biomarker that was elevated (P=0.01). Similar relationships existed for the endpoints of MI, CHF, and the composite, both at 30 days and through 10 months. In a

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Consensus Panel

BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Diseases

Marc A. Silver, MD, Chairman; Alan Maisel, MD
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Mandeep R. Mehra, MD; William Franklin Peacock IV, MD
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Panel Members

Marc A. Silver, MD, Chairman
Chairman and Clinical Professor
Department of Medicine and Heart Failure Institute
Advocate Christ Medical Center
Oak Lawn, IL

Alan Maisel, MD
Professor of Medicine
University of California, San Diego
San Diego, CA

Clyde W. Yancy, MD
Associate Professor of Internal Medicine and Cardiology
UT Southwestern Medical Center
Dallas, TX

Peter A. McCullough, MD, MPH
Consultant Cardiologist & Chief
Division of Nutrition & Prev. Medicine
William Beaumont Hospital
Royal Oak, MI

John C. Burnett, Jr., MD
Professor of Medicine
Mayo Clinic College of Medicine
Mayo Clinic
Rochester, MN

Gary S. Francis, MD
Professor of Medicine
Ohio State University
Cleveland Clinic Foundation
Cleveland, OH

Mandeep R. Mehra, MD
Chief, Cardiomyopathy and Heart Transplantation Center
Ochsner Clinic Foundation
New Orleans, LA

William Franklin Peacock IV, MD
Director, Clinical Operations
Cleveland Clinic Foundation
Cleveland, OH

Gregg Fonarow, MD
Professor of Medicine
Director, Ahmanson-UCLA Cardiomyopathy Center
Los Angeles, CA

W. Brian Gibler, MD
Professor and Chair, Department of Emergency Medicine
University of Cincinnati
University Hospital
Cincinnati, OH

David A. Morrow, MD
Assistant Professor of Medicine, Harvard Medical School
Director, TIMI Biomarker Core Laboratory
Brigham and Women's Hospital
Boston, MA

Judd Hollander, MD
Clinical Research Director
Department of Emergency Medicine
Hospital of the University of Pennsylvania
Philadelphia, PA

Subject Index

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BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Diseases

Among the most exciting developments in the field of heart failure in recent times has been the rediscovery of the natriuretic peptide system and its pleuripotent effects on cardiac structure and function. This is particularly true of its natriuretic and hemodynamic effects. There has been an explosion of the knowledge base seeking to understand the wide range of homeostatic, regulatory, and counter-regulatory functions in which the natriuretic peptide system participates. Additional interest has been stimulated by advances in technology such as point-of-care and core laboratory BNP assays and the use of the recombinant B-type natriuretic peptide nesiritide as a treatment option. Despite this recent interest, the available literature lacks a comprehensive expert review of the current science and roles of natriuretic peptides for diagnostic, prognostic, screening, treatment monitoring, and therapeutic purposes. More importantly, a summary updating and guiding the clinician on most of these advances was lacking. An expert Consensus Panel with basic, methodological, and clinical expertise was convened to summarize current knowledge in these areas and the findings and consensus statements are contained herein.
[CHF. 2004;10[5 suppl 3]:1–30]

"Illness is nothing else than a break of a body's harmony that has the endogenous tendency to reconstitute itself, an endeavor that the physician can only support by appropriate measures."

Hippocrates, 460–377 BC

Preface

We are fortunate to be living in this era of heart failure (HF) care. Most of our professional careers have encompassed the development, clinical validation, and application of therapies such as angiotensin-converting enzyme inhibition, aldosterone antagonism, and β-adrenergic blockade. We are also the generation of HF professionals who has trialed and is now applying therapies such as cardiac resynchronization, and for certain populations, routine defibrillation and ventricular assist.

Yet, all of these contributions notwithstanding, we have also witnessed perhaps the most important and far-reaching rediscovery of our careers, namely the notion that understanding and measurement of the natriuretic peptide system has the potential to improve care and outcome for patients with HF.

Perhaps the test of the importance of this rediscovery has been the explosion of the knowledge base seeking to understand the wide range of homeostatic, regulatory, and counter-regulatory functions in which the natriuretic peptide system participates. In many ways, we are like archeologists digging deep into an ancient, long-lost discovery and finding a major breakthrough bringing us one large step closer to the grail. Topping the list of important discoveries about the natriuretic peptide system, of course, have been the importance of the biomarker proteins as diagnostic tools for HF and the development of B-type natriuretic peptide (BNP) as therapy for HF patients.

As typically happens in science, there is an explosion of interest, and often emerging knowledge, that outstrips any organized understanding or infrastructure to guide us meaningfully. Frequently, in our professional lives, we have had the ability to do or measure "something" long before we worked our way to understanding an

Marc A. Silver, MD;[1] Alan Maisel, MD;[2] Clyde W. Yancy, MD;[3] Peter A. McCullough, MD, MPH;[4] John C. Burnett, Jr., MD;[5] Gary S. Francis, MD;[6] Mandeep R. Mehra, MD;[7] William Franklin Peacock IV, MD;[6] Gregg Fonarow, MD;[8] W. Brian Gibler, MD;[9] David A. Morrow, MD;[10] Judd Hollander, MD[11]

From the Department of Medicine and Heart Failure Institute, Advocate Christ Medical Center, Oak Lawn, IL;[1] University of California, San Diego, San Diego, CA;[2] Department of Internal Medicine/Cardiology, UT Southwestern Medical Center, Dallas, TX;[3] Division of Nutrition and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI;[4] Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN;[5] Cleveland Clinic Foundation, Cleveland, OH;[6] Cardiomyopathy and Heart Transplantation Center, Ochsner Clinic Foundation, New Orleans, LA;[7] Ahmanson-UCLA Cardiomyopathy Center, Los Angeles, CA;[8] Department of Emergency Medicine, University Hospital, Cincinnati, OH;[9] Brigham & Women's Hospital, Boston, MA;[10] Department of Emergency Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA[11]

Address for correspondence: Marc A. Silver, MD, Chairman and Clinical Professor, Department of Medicine and Heart Failure Institute, Advocate Christ Medical Center, 4440 West 95th Street, Suite 319 South, Oak Lawn, IL 60453-2600

E-mail: marc.silver@advocatehealth.com

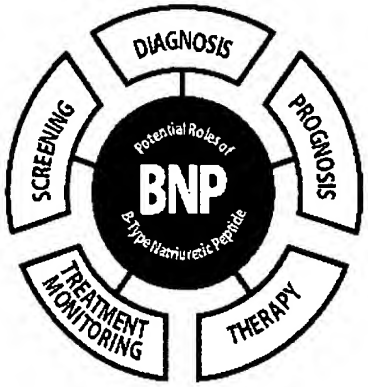

Figure 1. Hub and spoke conceptualization of some of the potential roles of B-type natriuretic peptide (BNP).

optimal utilization of that resource or technology, e.g., heart transplant and percutaneous coronary angioplasty.

We have at hand a similar situation with the BNP system: the knowledge base and emerging information is plentiful—the consensus about its application today is sparse. Therein lies the genesis of the BNP Consensus Panel 2004. Indeed, this work was not created by a lack of guideline process—that is, a distinct process with distinct goals. The BNP Consensus Panel was formed to review the science and technology of BNP measurement and administration and provide a reasonable framework for understanding where we are and where we need to go. It is very much an initial infrastructure as well as a work in progress.

Thus, an expert panel was gathered by selecting clinicians and scientists with expertise with the natriuretic peptide system. The purposes were two-fold: (1) to provide clinicians with an updated review of this important rediscovery and (2) to provide expert opinion and consensus statements on how the rediscovery can be currently applied and where it may lead us in the near future.

The panel of clinicians and scientists began with a draft document and then, through an accelerated series of electronic interactions, a Web-based document-editing process, and a single face-to-face meeting, sculpted the current document. During such discussions, the Panel determined that certain topics warranted consensus and as such the Panel has provided distinct "Consensus Statements" throughout the paper. Further, the Panel also felt strongly that we wanted to emphasize the synergy between the peptides as both a diagnostic and a therapeutic tool; therefore, the document discusses treatment with BNP. Once completed, the paper was peer-reviewed by members of the editorial board of the Journal and their comments addressed. Such editorial board members remarked at the unbiased tenor of the paper. The Panel is appreciative of the multiple sponsorships provided and the resulting balanced perspectives obtained in the preparation of this paper.

We also knew that with the rapidity and interest surrounding the natriuretic peptide system, the document would become outdated as time passes. The Panel may provide periodic updates to this paper to address advances in the field. Finally, recognizing that our ultimate goal was to help the busy clinician understand the emerging science of natriuretic peptides and not disregard its value simply for lack of a clear distillation, the Panel intends to disseminate the document in additional formats and media.

We trust the information contained herein is useful and ultimately helps all of us meet our goals for earlier detection and treatment of patients with, or at risk for, HF. For the many hours of collaborative work and actual and virtual interaction, I extend my gratitude and appreciation to all those who participated; every bit of expertise and contribution can be felt in the document.

Marc A. Silver, MD, Chairman
BNP Consensus Panel 2004

Introduction and Background

Since its approval by the United States Food and Drug Administration (FDA) in November 2000, the interest in clinical and research applications in BNP testing in the United States and around the world has been staggering. In the United States alone, it is estimated that up to 70% of all hospitals utilize BNP testing.[1] Indeed, understanding the role and nature of the natriuretic peptide system in health and disease is occupying the minds of clinicians and investigators alike. Initially focused on the emergent, bedside diagnosis of HF, subsequent research has supported the value of testing BNP in settings outside of the emergency department (ED). Not only is it a useful adjunct to diagnose and monitor patients with HF, but recent studies now suggest that BNP provides independent prognostic information predicting risk of rehospitalization and mortality. In addition, BNP might have a role in screening high-risk patients for the presence of underlying cardiac dysfunction.

The popularity of any new test has a potential downside—too many tests may be ordered for less than appropriate reasons. Physicians have voiced concern over how best to integrate BNP testing in the clinical arena so that they can make informed decisions in diagnosing and managing patients. Extrapolation of peer-reviewed literature is sometimes needed, and it is here that clinical acumen plays a part. The statements presented in this manuscript are done so by a consensus that was structured on evidence-based medicine intermingled with clinical judgment; the authors having all used BNP testing in their practice. It should be made clear at the outset that BNP is not a stand-alone test. It is always of greatest value when it complements the physician's clinical skills along with other available testing.

It is with these issues in mind that this BNP Consensus Panel 2004 was formed. Similar to the typical guideline recommendation process where recommendations are based predominantly on the availability of clinical outcome trials and expert opinion, this process includes all pertinent available trial data as well as expert consensus. The distinct purposes are to:

- Provide consensus statements for the clinician or health care service planner for consideration of incorporating BNP into clinical use or into a biomarker panel.

- Provide an up-to-date distillation of the current and proposed application of BNP as a biomarker and therapeutic agent. Areas of specific discussion will center around:
  - Diagnosis;
  - Prognosis;
  - Screening;
  - Treatment monitoring; and
  - Therapy/administration as a therapeutic agent (Figure 1).
- Provide an overview of BNPs in their diagnostic and therapeutic role and possibly stimulate further research with this important biomarker.

This paper integrates evidence-based outcome data with expert opinion in providing recommendations for clinical use of BNP. We hope that the document will stimulate the continued investigation of the natriuretic peptide system, exploring its potential to facilitate earlier detection and prevention of disease.

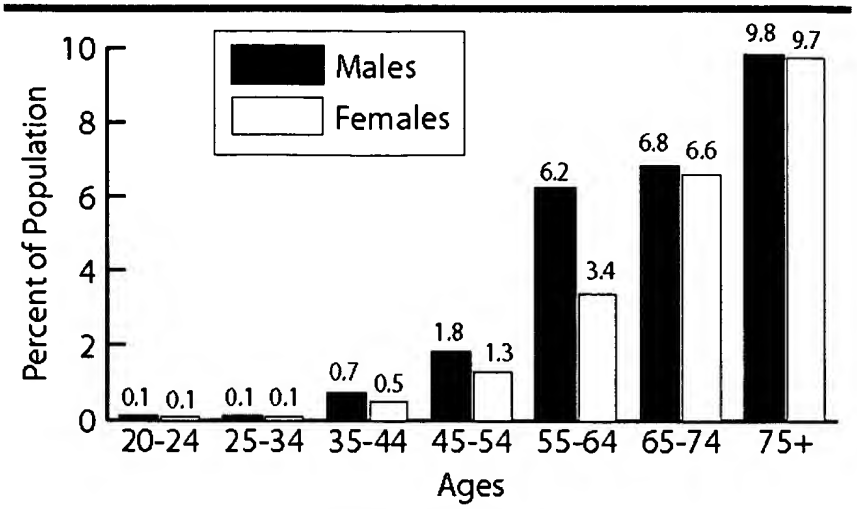

Figure 2. Increasing prevalence of heart failure by age and gender as demonstrated in the American Heart Association heart disease and stroke statistics. Reprinted from *Journal of the American College of Cardiology*, 39, McCullough PA, Philbin EF, Spertus JA, et al., Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study, 60–69, Copyright 2002, with permission from American College of Cardiology Foundation.

Background on HF and Need for Better Ways to Evaluate. Over the past 100 years, cardiovascular disease (CVD) has become a leading cause of morbidity and mortality worldwide. At the beginning of the last century, CVD accounted for <10% of all deaths worldwide. With decreasing mortality from infectious diseases and accidents, there has been a substantial increase in CVD risk factors, such as obesity and diabetes. Additonally, the use of disease-modifying agents like angiotensin-converting enzyme inhibitors and β blockers that improve survival rate after acute myocardial infarction (MI) and subsequent development of HF has increased. At the beginning of the 21st century, CVD now accounts for nearly one half of all deaths in the developed world and 25% in the developing world. By 2020, CVD is projected to be the cause of 25 million deaths each year and will surpass infectious disease as the world's leading cause of death and disability.

Figure 2 shows the increasing incidence and prevalence of HF in the United States according to the Centers for Disease Control and Prevention. In the United States alone, about 950,000 people die of CVD each year. CVD accounts for nearly 40% of all deaths, which amounts to one death every 33 seconds. It is a leading cause of death for both men and women, and although more common among people aged 65 years or older, the number of sudden deaths from heart disease among people aged 15–34 years has increased. Also, about 61 million Americans, almost one fourth of the population, live with CVD, of which 4.7 million are symptomatic HF patients. This number is expected to increase to an estimated 10 million by 2037, which makes coronary artery disease (CAD) a leading cause of premature, permanent disability in the US workforce.[2,3] There are almost 6 million hospitalizations each year due to CVD, including HF. The cost of heart disease and stroke in the United States in 2003 was projected to almost match the current federal yearly budget deficit—a staggering $351 billion, including health care expenditures and lost productivity from death and disability. The cost of HF itself is $56 billion a year, 70% of which is due to hospitalization. In a study of 17,000 survivors of hospitalization for HF, it was shown that almost half were readmitted within 6 months, and close to 16% were readmitted at least twice.[4]

Biology and Physiology of Natriuretic Peptides. ***Physiology of Natriuretic Peptides.*** In addition to being an extremely efficient and resilient pump, the human heart is an important endocrine organ that functions together with other physiological systems to control fluid volume. Cells of the heart manufacture a family of structurally related peptide hormones, collectively termed the natriuretic peptides that include atrial natriuretic peptide (ANP) and brain or BNP. Structures of the ANP and BNP are shown in Figure 3 along with a related peptide, C-type natriuretic peptide (CNP). Although CNP is structurally related to ANP and BNP, this peptide is secreted mainly by the vascular endothelium and will not be discussed further. ANP and BNP are encoded by separate genes, and like many physiologically active proteins, are synthesized in the form of precursors. Release of the natriuretic peptides is stimulated by volume overload[5]; these hormones have powerful diuretic, natriuretic, and vascular smooth muscle relaxing actions. The natriuretic peptides are natural antagonists for the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).[5–7]

Biochemistry of Natriuretic Peptides. The natriuretic peptide system involves secretion of peptides in response to many triggers, including wall stretch,

Table I. Comparison of the Biochemical and Physiological Characteristics of Natriuretic Peptides

	ANP	BNP
Peptide length	28 Amino acids	32 Amino acids
Cognate receptor	NPR-A, NPR-C	NPR-A, NPR-C
Precursor	PreproANP (151 aa)	PreproBNP (134 aa)
Prohormone (precursor without the signal sequence)	ProANP (126 aa)	ProBNP (108 aa)
Storage of prohormone	Atrial granules	Preferentially secreted in the ventriculum without storage
Major circulating peptide fragments	NT-proANPs$_{(1-30,\ 31-67,\ 79-98)}$ ANP$_{(99-126)}$	NT-proBNP$_{(1-76)}$ BNP$_{(77-108)}$
Biologically active hormone (containing the disulfide bridge)	ANP$_{(99-126)}$	BNP$_{(77-108)}$
Plasma half-life	3 Minute	21 Minute
Release stimulus	Atrial transmural tension	Ventricular wall tension
Synthesis site	Cardiac atrium	Cardiac ventricle
Physiological actions	Natriuresis vasodepression inhibition, RAA system antimitogenesis	Natriuresis vasodepression inhibition, aldosterone ? antimitogenesis

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; NPR=natriuretic peptide receptors; NT=N-terminus; RAA=renin-angiotensin aldosterone

ventricular dilation and/or increased pressures, all resulting from fluid overload. Activation of the natriuretic system also results from lowering blood volume and blood pressure (BP). Table I presents a listing and summary of the biochemical characteristics of natriuretic peptides.

Biosynthesis and Secretion of BNP. BNP is derived from the 134-aa precursor preproBNP. Upon release stimulation, a 26-aa signal peptide sequence is cleaved from the precursor's N-terminus to produce proBNP$_{1-108}$. This hormone is further cleaved by a membrane-bound serine protease (corin), into an N-terminal proBNP$_{1-76}$ fragment and the active C-terminal 32 amino acid peptide hormone$_{77-108}$ termed BNP. The N-terminal proBNP fragment has also been proposed as a clinical marker of HF, and clinical application and assays for this proBNP fragment have been developed and recently reviewed.[8]

BNP is preferentially produced and secreted by the ventricles of the heart without storage in granules. Therefore, regulation of BNP synthesis and secretion occurs mainly at the gene level.[9] However, both ANP and BNP can be synthesized in the atrium, ventricles, or both under pathologic conditions. In fact, fluid overload may cause rapid BNP production in both heart chambers, and production in the atrium may exceed the amount of ANP.[10]

Analytical and Assay Characteristics. ***Preanalytical Determinants. Which Natriuretic Peptide Should Be Measured, ANP or BNP?*** Compared with ANP, BNP has emerged as a superior marker for HF and left ventricular (LV) dysfunction. The longer half-life, rapid production and stable release pattern, in additon to activation at the gene level, and the fact that greater amounts are produced in LV tissue has made BNP the marker of choice.[5] Physiologically, a two-fold increase in plasma ANP is sufficient to cause negative sodium balance, a fall in systolic and diastolic BP, and an increase in heart rate[11]; however, BNP has a two- to three-fold more powerful effect on natriuresis and BP lowering than ANP.[12] Under normal conditions, blood concentrations of BNP are lower than ANP, but as the severity of volume overload progresses, such as, from HF, plasma BNP increases and frequently exceeds ANP concentrations.[11] There is a positive correlation between blood BNP concentrations and LV end diastolic pressure, and an inverse correlation to LV function.[13] In a study by Cowie et al.,[14] BNP showed the greatest predictive power as an indicator of HF when compared with ANP or N-terminus proANP (NT-proANP). For this reason, BNP is considered to be better than NT-proANP, and both have advantages over ANP.

Physiologic Action of BNP and ANP. The main physiological function of the natriuretic peptides is homeostasis and protection of the cardiovascular and other systems from the effects of volume overload. After release into circulation, the effects of BNP and ANP are modulated at target sites and in the kidney by three specific natriuretic peptide receptors (NPRs). These receptors are located on cell membranes and are termed NPR-A, NPR-B, and NPR-C. After binding the natriuretic peptides, both NPR-A and NPR-B mediate physiological actions across the membrane through guanylate cyclase, present in a variety of tissues, including the endothelium of large vessels and, for NPR-B, the brain. After binding to the extracellular NPR site, there is transmembrane communication that catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP).[15] cGMP has potent vasodilatory actions and acts as a second messenger for the natriuretic peptides. In addition to the effects mediated by cGMP, BNP causes a shift in intravascular fluid from the capillary bed into the interstitium,

which induces intravascular volume contraction and a decrease in BP.[16-18] In addition, the natriuretic peptides, specifically BNP, may be viewed as natural antagonists of the RAAS because they counteract the sodium conserving, vasoconstriction, and volume retention activities of the RAAS. BNP also appears to inhibit release of renin from kidney cells and aldosterone from adrenal cells, thus limiting the amount of these hormones released. Figure 4 illustrates how the natriuretic peptide system and the RAAS counterbalance each other in regulation of fluid volume and arterial pressure.

BNP and other circulating natriuretic peptides are also degraded by neutral endopeptidase, which opens the ring structure of BNP and ANP, thus inactivating the molecule.[19] This endopeptidase has wide tissue distribution, including the kidneys, lung, and brain. The affinity is highest for CNP, followed by ANP, which is much higher than for BNP.

Biologic Determinants of BNP Measurements. Blood levels of natriuretic peptides are affected by a variety of physiological factors, such as circadian rhythm, age, exercise, and body posture.[5] Drugs including diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists, sex and thyroid hormones, glucocorticoids, as well as sodium intake, and many clinical conditions can also modify circulating levels of cardiac hormone peptides.

Plasma BNP concentrations increase with age and are higher in women than men both with and without cardiac dysfunction.[20,21] The increase in natriuretic peptides with age may be due to the decline in myocardial function typical of senescence[22] and/or to reduction in clearance of natriuretic peptides related to the aging process. BNP concentrations for treated hypertensive patients did not show any statistically significant effect from the age-matched control population.[20] It has been suggested that age- and gender-specific reference intervals should be considered for routine interpretation of BNP values.

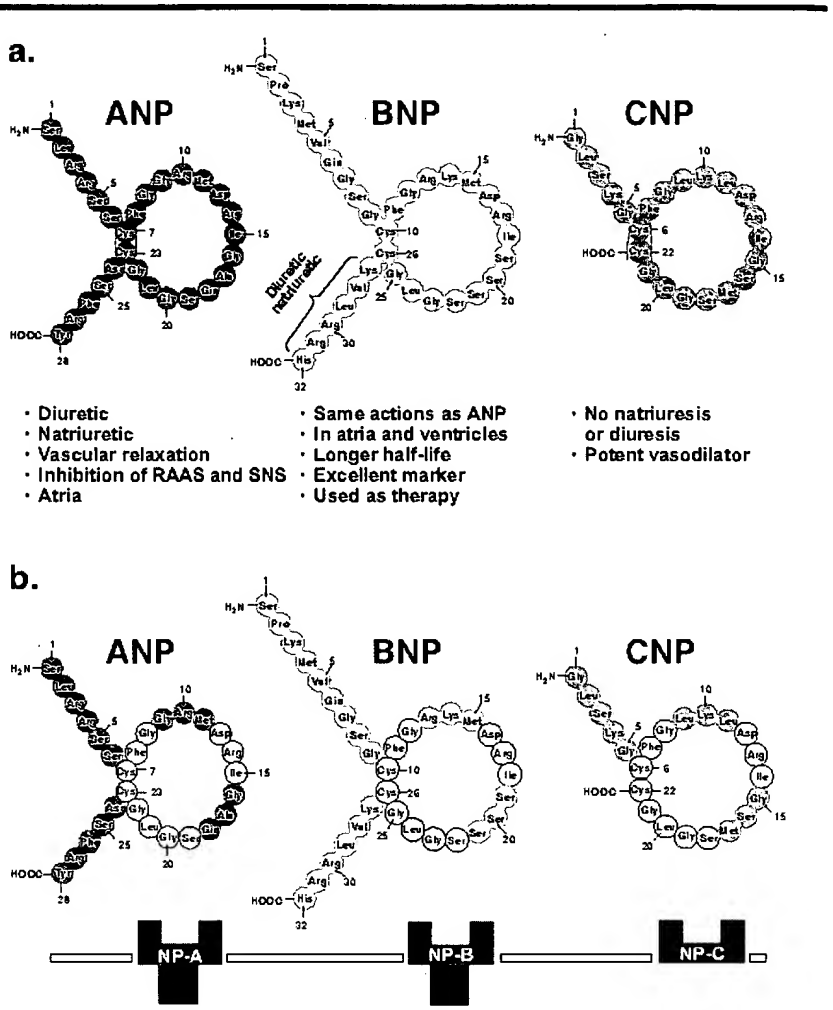

Figure 3a. The natriuretic peptides: structure and function. ANP=A-type natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

Figure 3b. These are the molecular structures of the natriuretic peptides ANP, BNP, and CNP. Below are the natriuretic peptide receptors NP-A, NP-B, and NP-C. The ring structure of the natriuretic peptides is essential for receptor binding. While ANP and CNP have high affinity for the receptors, no particular receptor has been discovered for BNP. In addition to receptor binding, natriuretic peptides are cleared from the bloodstream by enzymatic degradation. ANP and CNP have a higher affinity for the enzyme responsible for this degradation. These factors result in a longer half-life for BNP, thus making it useful as a detectable marker for heart failure.

BNP Assays. Initial BNP assays were radioimmunoassays that required an extraction step. They suffered a number of limitations including:

- A delay in reporting results (up to 24 hours were required to complete the assay);
- Highly skilled medical technologists required to perform with high precision;
- Large sample volume; and
- Labor costs are much higher than for automated assays.

Attempts were made to overcome these problems and develop more direct BNP assays.[23] Currently, there are four BNP assays that are FDA approved. Some characteristics of the newly developed automated BNP assays are summarized in Table II.

BNP concentration in plasma samples was originally measured by a direct solid phase assay using the Shionoria BNP IRMA kit (Shionogi & Co., Ltd., Osaka, Japan). This sandwich assay employs two different monoclonal

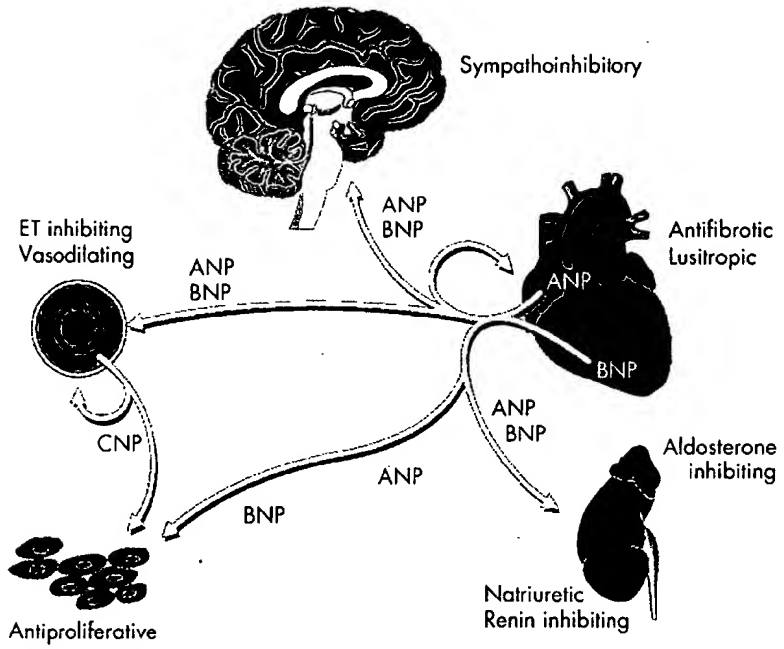

Figure 4. Diagram of interaction of heart, kidney, vasculature, brain, and renin-angiotensin-aldosterone system with natriuretic peptide system. ET=endothelin; ANP=A-type natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide

antibodies, which recognize sterically remote epitopes. The measurable range is from 2–2000 ng/L.[24] The within-day and total coefficient of variations were both 8% and were consistent across concentrations of BNP.

The currently available BNP assays and their platforms are summarized in Table II. The first BNP assay cleared by the FDA is the Triage BNP Test (Biosite, Inc., San Diego, CA) which is a point-of-care assay, uses whole blood or plasma and produces results in ≈15 minutes.[25] A chemiluminescent sandwich immunoassay (Bayer HealthCare Diagnostics, Tarrytown, NY) for BNP is run on the ADVIA Centaur and ACS:180 platforms. A microparticle-based immunoassay (Abbott Laboratories, Abbott Park, IL) for BNP is run on the AxSYM platform. A chemiluminescent immuno-enzymatic assay (Biosite, Inc., San Diego, CA) for BNP is run on the following Beckman Coulter platforms: Access, Access 2, Synchron LXI and the UniCel DXI. Another peptide assay is an electrochemiluminescent assay (Roche Diagnostics, Indianapolis, IN) available for measuring NT-proBNP. The reference ranges for BNP and NT-proBNP vary depending on a number of factors. The suggested decision cut-point for the detection of HF for the BNP assay is 100 pg/mL in the dyspneic patient. For the NT-proBNP assay, the recommended decision cutpoint is 125 pg/mL for both genders under 75 years of age and 450 pg/mL for 75 years and older.

Differences Between NT-proBNP and BNP. While the purpose of this consensus is to offer a review and practical recommendations with regard to mainly BNP, we briefly comment on NT-proBNP, as it has recently been approved by the FDA. While it is likely that both BNP and NT-proBNP will have a place in the diagnosis, prognosis, and management of HF, the two molecules are not identical. Table III lists important differences between BNP and NT-proBNP. Differences that may have clinical relevance are related to excretion, as well as the differences in half-life. While the scope of this paper is such that NT-proBNP will not be discussed at length, it is clear that

Table II. Characteristics of BNP Assays

Vendor	Platform	Technology	Marker	Imprecision	Dynamic Range	Cutoff (pg/mL)
Abbott Laboratories, Abbott Park, IL	AxSYM	Microparticle enzyme immunoassay	BNP	Total %CV range: 6.5–9.4	0–4000	100
Bayer HealthCare Diagnostics, Tarrytown, NY	ADVIA Centaur ACS:180	Direct chemiluminescent sandwich immunoassay	BNP	Total %CV range: 2.3–4.7	0–5000	100
Biosite, Inc., San Diego, CA	Triage BNP	Single use fluorescence immunoassay device	BNP	Total %CV range: 9.9–12.2	0–5000	100
Biosite, Inc., San Diego, CA	Beckman Coulter: Access, Access 2, Synchron LXI, UniCel DXI	Two-site chemiluminescent immuno-enzymatic assay	BNP	Total %CV range: 2.1–6.7	0–5000	100
Roche Diagnostics, Indianapolis, IN	Elecsys	Electrochemiluminescent immunoassay	NT-proBNP	Total %CV range: 3.6–5.8	0–35,000	<75 yr: 125 >75 yr: >450

BNP=B-type natriuretic peptide; CV=co-efficient of variation; NT=N-terminus; Imprecision is listed in total %CV from vendor package insert.

Table III. B-Type Natriuretic Peptide (BNP) vs. NT-proBNP Assay for Heart Failure

Characteristic	BNP	NT-proBNP
Analyte detected	$BNP_{(77-108)}$	$NT\text{-}proBNP_{(1-76)}$
Molecular weight	3.5 Kilodaltons	8.5 Kilodaltons
Hormonally active	Yes	No, inactive peptide
Genesis	Cleavage from proBNP	Cleavage from proBNP
Half-life	20 Minutes	120 Minutes
Major clearance mechanism	Natriuretic peptide receptors	Renal clearance
Increases with normal aging	+	++++
Approved cutoff(s) for CHF diagnosis	100 pg/mL	Age <75: 125 pg/mL Age ≥75: 450 pg/mL
Available at the point-of-care	Yes	No
Studies completed	1370	39
Entry on US market	November 2000	December 2002

NT=N-terminus; CHF=congestive heart failure; ©MedReviews, LLC. Reprinted with permission of MedReviews, LLC. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. *Rev Cardiovasc Med.* 2003;4(suppl 4):S13–S19. *Reviews in Cardiovascular Medicine* is a copyrighted publication of MedReviews, LLC. All rights reserved.

work is still needed to establish the data and the algorithms to be used in clinical practice with this marker.

Recent reports indicate that there is minimal loss of BNP in blood collected using EDTA as the anticoagulant. BNP is more stable in plastic tubes than glass tubes. Some investigators have indicated that blood can remain at room temperature for up to 48 hours before separation.[26,27] BNP has also been found to be stable for several months at –20°C[27]; however, whole blood or EDTA plasma specimens are stable for 4–24 hours at room temperature and for 8–24 hours at 4°C depending upon the BNP assay used.[20]

Diagnosis

BNP Testing and the Diagnosis of Symptomatic HF. ***Role of BNP Levels in the Diagnosis of Dyspnea and HF in ED Settings.*** Although there have been tremendous advances in our understanding of the pathophysiology and treatment of HF, diagnosis of the disease still remains difficult. For the acutely ill patient presenting to the ED with dyspnea, an incorrect diagnosis could place him or her at risk for both morbidity and mortality.[28] Therefore, the ED diagnosis of HF must be rapid and accurate. Unfortunately, the signs and symptoms of HF are nonspecific.[29] A helpful history is not often obtainable in an acutely ill patient, and dyspnea, a key symptom of HF, may also be a nonspecific finding in the elderly or obese patient in whom comorbidity with respiratory disease and physical deconditioning are common.[30] Routine laboratory values, electrocardiograms, and x-rays are also not accurate enough to always make the appropriate diagnosis.[30–33]

Multiple studies establish the value of BNP for facilitating the diagnosis of HF in patients presenting with dyspnea. Davis and colleagues[33] first measured levels of the natriuretic hormones ANP and BNP in 52 patients presenting with acute dyspnea. They found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection fraction levels or ANP plasma concentrations.

Dao et al.[34] were the first to use the BNP assay to evaluate 250 patients presenting to an urgent care center with the chief complaint of dyspnea. Physicians assigned to the unit were asked to make an assessment of the probability (low, medium, or high) for each patient with dyspnea and were blinded to the results of BNP measurements. The finding that BNP levels were the strongest predictor of those who had HF served as the foundation for the Breathing Not Properly study,[35] the first large-scale, multinational, prospective study using BNP levels to evaluate the causes of dyspnea.

In this study of 1586 patients who came to the ED with acute dyspnea, patients' BNP levels were measured upon arrival, and the emergency physicians, blinded to BNP levels, were asked to assess the probability of the patient having HF.[36] Two independent cardiologists also blinded to the BNP levels later reviewed all clinical data and standardized scores to produce a "gold standard" clinical diagnosis for each patient. BNP levels by themselves were found to be more accurate predictors of the presence

Consensus Statement 1: General Comments on BNP Measurement and Molecule Selection

1.1 The laboratory should perform BNP testing on a continuous 24-hour basis with a turn-around-time (TAT) of 60 minutes or less. The TAT is defined as the time from blood collection to notification of test result to physician or caregiver. Either central laboratory instrumentation or point-of-care testing systems are acceptable.

1.2 In considering natriuretic peptide measurements, one needs to carefully consider laboratory and biologic variation, including gender, sex, obesity, and renal function.

1.3 The results of natriuretic testing are dependent on the type of test you are obtaining. NT-proBNP and bioactive BNP are NOT interchangeable.

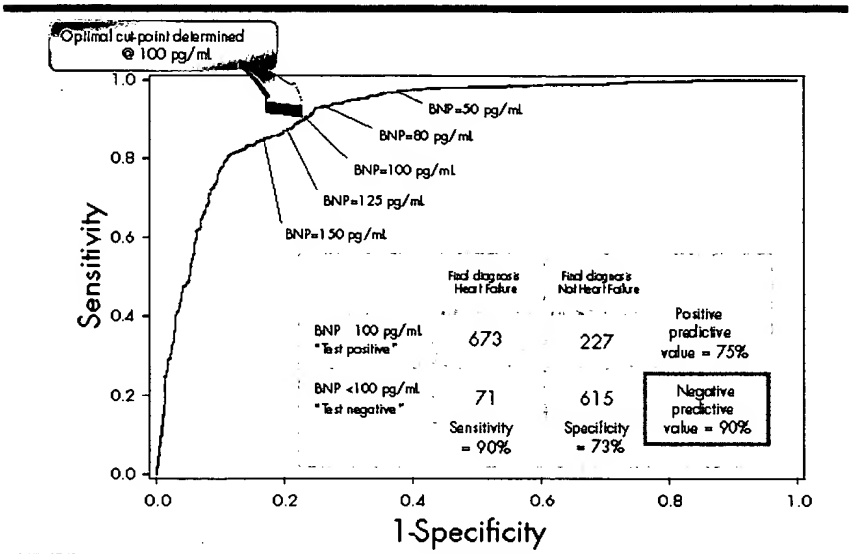

Figure 5. Illustration of the specificity, sensitivity, and accuracy of a B-type natiuretic peptide (BNP) cutoff value of 100 pg/mL for differentiating congestive heart failure from other causes of dyspnea. Reprinted with permission from *N Engl J Med.* 2002;347(3):161–167.[35]

or absence of HF than any history, physical findings, or laboratory values. BNP levels were much higher in patients with subsequent HF than in those with noncardiac dyspnea (675 pg/mL vs. 110 pg/mL). A BNP cutoff value of 100 pg/mL had a sensitivity of 90% and a specificity of 76% for differentiating HF from other causes of dyspnea, and a cutoff level of 50 pg/mL had a negative predictive value of 96% (Figure 5). There was a 43% indecision rate among physicians in the ED trying to make a diagnosis in patients with dyspnea (Figure 6). BNP levels added significantly to the tools of the clinician. Had BNP levels been available, the indecision rate would have been reduced to 11%. In multivariate analysis, BNP levels always contributed to the diagnosis, even after consideration of the history and physical exam.

Using BNP Levels to Help Triage Patients Presenting to the ED With HF. While BNP levels aid in the diagnosis of HF in the ED, there might also be a role for using BNP levels to help make triage decisions, i.e., who should be admitted directly vs. who might be treated and then discharged. The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT)[37] demonstrated a disconnect between the perceived severity of HF cases by emergency physicians and severity as determined by BNP levels. In the first phase, 464 patients visiting EDs with complaints of breathing difficulty had BNP measurements taken on arrival, then every 3 hours while in the ED, as well as at the time of hospital admission or discharge from the ED. Physicians were only informed whether the initial BNP level was greater than or less than 100 pg/mL. They were blinded to subsequent BNP results. Patients discharged from the ED had higher BNP levels than those admitted to the hospital. The median BNP level for discharged patients was 976 pg/mL, 27% higher than the median BNP level for patients who were admitted to the hospital (766 pg/mL). Approximately 90% of all patients were admitted to the hospital from the ED. Of the admitted patients, 11% had BNP levels <200 pg/mL, which is indicative of less severe HF. Mortality for these patients was 0% at 30 days and only 2% at 90 days. Of the 10% of patients discharged from the ED, 78% had BNP levels >400 pg/mL. At 30 days, mortality in these patients was 0%, but at 90 days, mortality was 9%. There was no mortality in those patients discharged with BNP levels <400 pg/mL.

The B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) Study,[36] which was done in Switzerland, extended the value ascertained from the Breathing Not Properly Study[38] in terms of cost-effectiveness of using BNP levels throughout the diagnostic evaluation and hospitalization phases of HF. In this study, the investigators

Consensus Statement 2: Using BNP Levels to Help Triage Patients Presenting to the ED With Dyspnea

2.1 BNP is of diagnostic utility in the evaluation of patients with acute dyspnea. Thus, in new patients presenting with dyspnea to an emergency setting, a history, physical examination, chest x-ray, and electrocardiogram should be undertaken together with laboratory measurements that include BNP. Current data suggest the following statements:

- **2.1.1** As BNP levels rise with age and can be affected by gender, comorbidity, and drug therapy, the plasma BNP measurement should not be used in isolation from the clinical context.
- **2.1.2** If the BNP is <100 pg/mL, then HF is highly unlikely; negative predictive value, 90%.
- **2.1.3** If the BNP level is >500 pg/mL, then HF is highly likely; positive predictive value, 90%.
- **2.1.4** For BNP levels of 100–500 pg/mL, one must consider the following: baseline BNP value elevated due to stable underlying dysfunction; right ventricular failure present from cor pulmonale; acute pulmonary embolism or renal failure.
- **2.1.5** Patients may present with HF and normal BNP levels or with levels below what might be expected. This can occur in the following situations: flash pulmonary edema, occurring <1–2 hours from symptom onset; HF up-stream from the left ventricle (i.e., acute mitral regurgitation from papillary muscle rupture); and obese patients (body mass index [BMI] >30 kg/m^2).

2.2 The complementary information that BNP provides may help objectively determine severity of HF and therefore be useful to help triage in deciding whether to admit, transfer to other sites of care, or discharge patients from the ED.

studied patients presenting to the ED with acute dyspnea who were randomly assigned to undergo either a single measurement of BNP or no such measurement. Participating clinicians were advised that a level of BNP <100 pg/mL made the diagnosis of HF unlikely, whereas a level >500 pg/mL made it highly likely. For intermediate levels, use of clinical judgment and adjunctive testing were encouraged. In this single-blind trial of 452 patients, rapid measurement of BNP in the ED was associated with decreases in the rate of hospital admission by 10 percentage points, the median length of stay by 3 days, and the mean total cost of treatment by about $1800, with no adverse effects on mortality or the rate of subsequent hospitalization. This carefully performed trial suggests that the use of BNP testing in the emergency evaluation of acute dyspnea can significantly improve both the quality and cost of care. These results are consistent with the Breathing Not Properly Study and showed that the use of a diagnostic test in the ED can reduce the use of hospital resources and associated costs by eliminating the need for other, more expensive tests, or by establishing an alternative diagnosis that does not require hospitalization.

Comorbidities and Special Issues Which Influence the Interpretation of BNP Levels. ***Renal Insufficiency.*** The Breathing Not Properly Multinational Study[38] was pivotal in establishing the correlations between estimated glomerular filtration rate (eGFR) and BNP in those with and without HF. This trial established that BNP values should not be interpreted in isolation and should be integrated with other findings in the diagnostic evaluation. Importantly, chronic kidney disease (CKD) does appear to influence the optimum cut-points for BNP in the diagnosis of HF. In general, as the CKD stage advances, a higher cut-point of BNP is needed. A cut-point of ≈200 pg/mL is reasonable for those with eGFR <60 mL/min. Using this approach, BNP would maintain a high level of diagnostic utility with an area under the receiver-operated characteristic (ROC) curve of >0.80 across all CKD groups.[38]

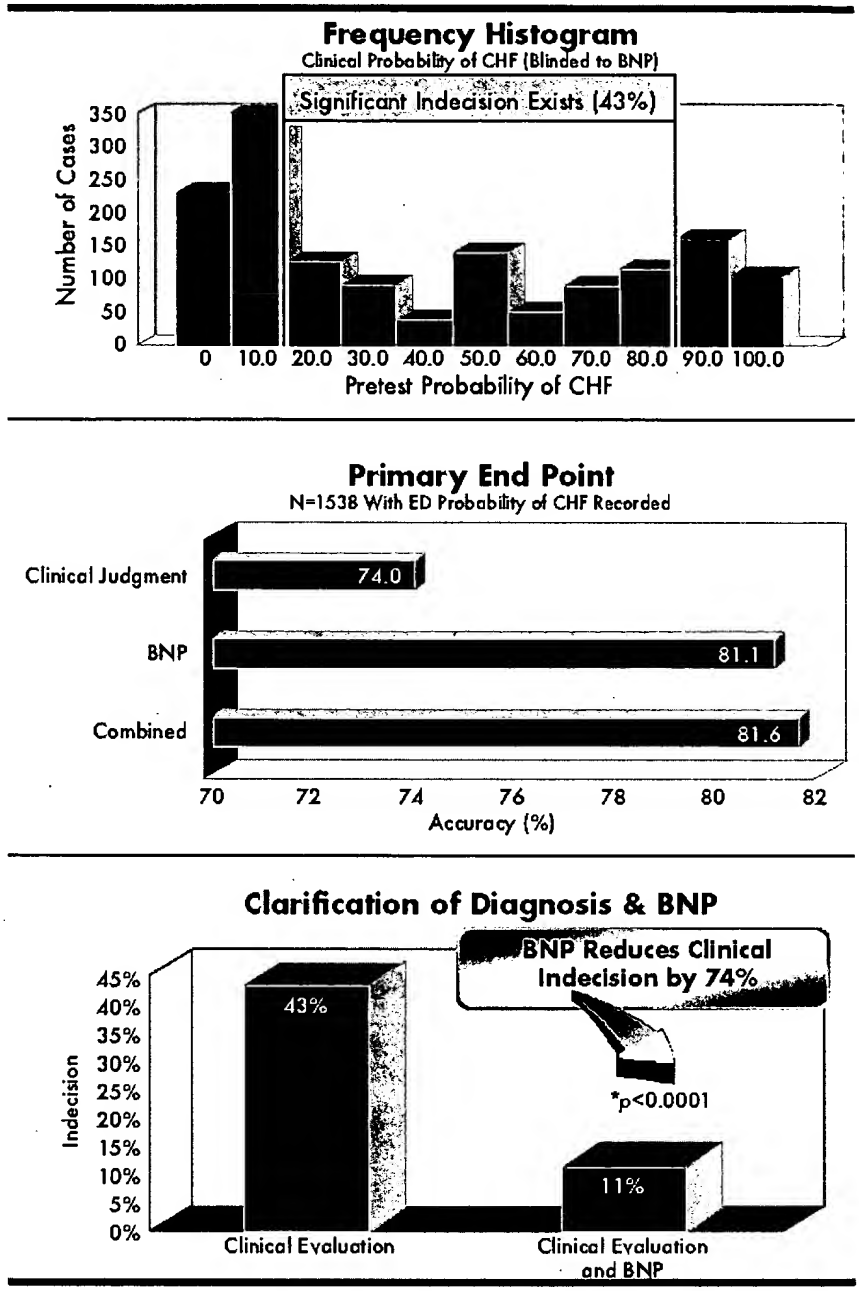

Figure 6. Illustration of indecision rate among physicians in the emergency department (ED) trying to make the diagnosis of dyspnea and the contribution of the B-type natriuretic peptide (BNP) levels cutting down the indecision rate. CHF=congestive heart failure. Adapted with permission from McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation*. 2002;106:(4)416–422.

It is possible that acute HF, with reduced renal blood flow, can result in elevations of serum creatinine and hence a falsely lower eGFR. In addition, chronic volume overload in patients due to CKD with or without HF can result in increased LV hypertrophy and wall tension, thus stimulating secretion of BNP. Multiple studies of systolic HF have demonstrated a decreased survival in those with reduced baseline eGFR.[39] It is unclear whether this is simply due to low cardiac output to the kidneys or if it signifies a unique cardiorenal syndrome conferring increased morbidity and mortality. Multivariate analyses have confirmed an independent relationship

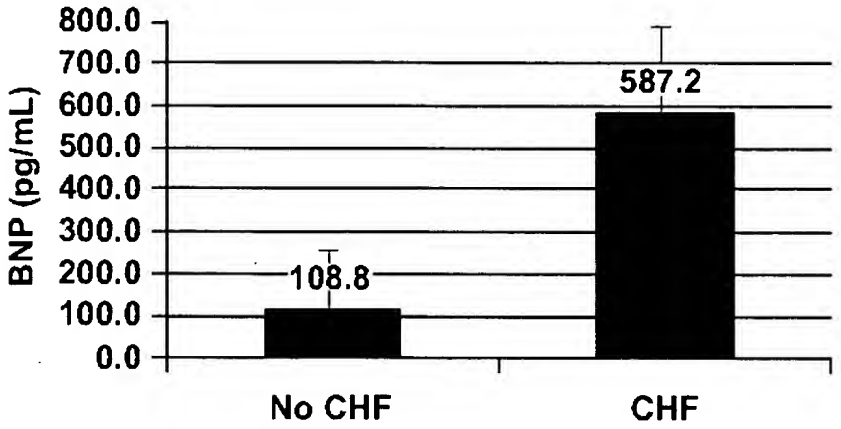

Figure 7. Mean ± standard deviations of B-type natriuretic peptide (BNP) values by final diagnosis in 417 adults with a history of asthma or chronic obstructive pulmonary disease with no history of congestive heart failure (CHF) who present with acute dyspnea. Reprinted from *Academic Emergency Medicine* <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=journals&list_uids=20159&dopt=full>, 10, McCullough PA, Hollander JE, Nowak RM, et al., Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department, 198–204, Copyright 2003, with permission from Society for Academic Emergency Medicine.

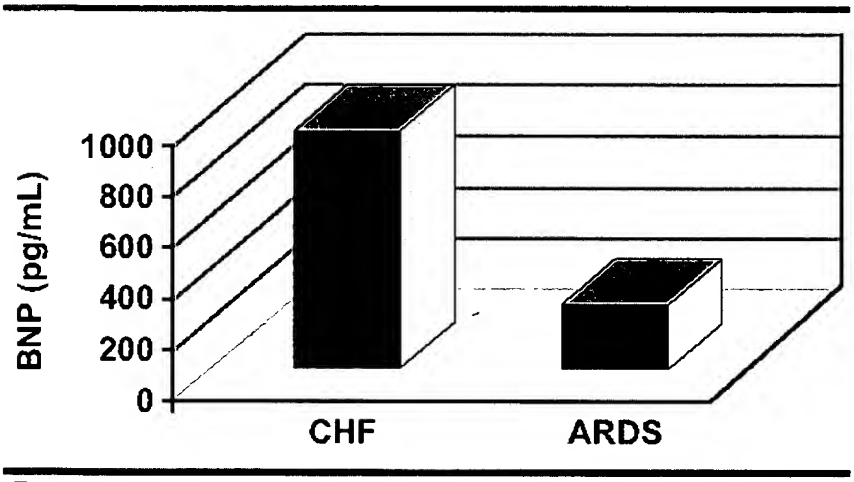

Figure 8. Comparison of the median B-type natriuretic peptide (BNP) level in congestive heart failure (CHF) patients with that of patients with acute respiratory distress syndrome (ARDS). Adapted with permission from *Circulation*. 2002;106:S3191.

between renal function and HF mortality; hence, further research into this important relationship is warranted.

Another application of BNP in CKD is measurement of BNP before and after hemodialysis. Several studies have found that BNP is predictably elevated in end-stage renal disease before dialysis and that it drops 20%–40% after a dialysis session.[40,41] It has been proposed that the BNP reduction ratio could be used as a measure of volume reduction and resultant decreased LV wall tension in those with end-stage renal disease. Current studies are underway to define the expected ranges of the BNP reduction ratio and to understand how it relates to measures of intravascular volume, total body water, and symptom scores.

Pulmonary Disease With/Without Associated Cardiac Disease. The presence of concomitant pulmonary disorders does not diminish the utility of BNP in distinguishing patients with HF from those without HF, as long as one uses good clinical judgment and appropriate ancillary testing.

Morrison et al.[42] were able to show that rapid testing of BNP could help differentiate pulmonary from cardiac etiologies of dyspnea. Some types of pulmonary disease, such as cor pulmonale, lung cancer, and pulmonary embolism, have elevated BNP levels, but these patients do not have BNP elevated to the extent of those with dyspnea from HF. In a substudy of Breathing Not Properly[43] (Figure 7), it was demonstrated that of 417 subjects with a history of asthma or chronic obstructive pulmonary disease (COPD) without a history of HF, 21% were found to have newly discovered HF. Only 37% were identified by the clinician in the ED, while a BNP >100 pg/mL identified 93%. Additionally, BNP levels >100 pg/mL provided diagnostic information beyond that obtained from individual chest radiographic indicators.[44]

Consensus Statement 3: Comorbidities and Special Issues That Influence the Interpretation of BNP Levels

- **3.1** There is an alteration in BNP with chronic renal insufficiency (estimated GFR below 60 mL/min), with a likely recalibration of the cutoff value to approximately 200 pg/mL. However, BNP is helpful in the evaluation of dyspnea when it is very low or high. NT-proBNP has a greater correlation with eGFR than BNP, hence levels can be elevated even with the normal age related decline of renal function in the eGFR 60 mL/min–90 mL/min range.
- **3.2** When the eGFR is below 60 mL/min, NT-proBNP can be considerably elevated and in this setting its utility in the evaluation of HF is unknown.
- **3.3** Baseline BNP levels might therefore be important in dialysis patients, as changes above baseline likely represent changes in volume. Thus a pre-dialysis BNP level might help determine the amount of volume to be removed. As of now, there is no good evidence that monitoring BNP levels during dialysis will help make correct decisions as to how long one should keep dialysis going. The effect of renal insufficiency on BNP may help determine the intensity of dialysis therapy.

Because BNP levels have been a useful surrogate of wedge pressure and are useful in differentiating HF from lung disease, they may be of value in differentiating noncardiogenic from cardiogenic pulmonary edema.[45] BNP levels were obtained in 35 patients with acute respiratory distress syndrome (ARDS) and from 42 patients hospitalized for severe dyspnea with the diagnosis of HF. The median BNP level in patients with HF of 773 pg/mL was significantly higher than patients with ARDS (123 pg/mL; $p<0.001$) (Figure 8). The area under the ROC curve using BNP to differentiate HF from ARDS was 0.90 (0.83–0.98; $p<0.001$). At a cut-point of 360 pg/mL, there was 90% sensitivity, 86% specificity, 89% positive predictive value, and a 94% negative predictive value (accuracy=88%) for ARDS vs. HF. In the Breathing Not Properly Multinational Study, there were 417 patients who had a history of lung disease and no history of HF who presented with acute dyspnea. The final adjudicated diagnosis was HF in 20.9% of cases.

Approximately one third of these "latent HF" cases were identified by the emergency physician, one third had cor pulmonale, and one third appeared to have the wrong diagnosis by past history and current ED evaluation. Importantly, BNP at a cut-point of 100 mg/dL would have identified 93.1% of these cases. Thus, in patients with established lung disease (COPD or asthma), when BNP is added to the dyspnea evaluation, it provides a yield of approximately 20% for latent HF. The diagnoses now present therapeutic opportunities for HF therapy including agents which block the RAAS, diuretics, and β blockers as tolerated.

In a study of 110 angiographically proven pulmonary emboli cases, one third of the patients had a BNP level ≥75 pg/mL.[46] Importantly, these cases with an elevated BNP in the upper normal range or above 100 pg/mL had a higher mortality than the first two tertiles of BNP values of <8.7 pg/mL and 8.7–75 pg/mL, respectively.[47] Furthermore, in an echocardiographic study, BNP elevations were associated with right ventricular (RV) dilation and dysfunction due to pressure overload in the setting of pulmonary embolism. It appears that BNP will not be an adequate screening test for pulmonary embolism; however, in the setting of a suspected or confirmed embolic event, an elevation of BNP indicates RV pressure overload and a higher overall mortality.

Finally, BNP levels are closely related to functional impairment of patients with primary pulmonary hypertension and parallel the extent of pulmonary hemodynamic changes and right HF.[48] It is speculated that serial measurements of BNP may help improve the management of these patients.

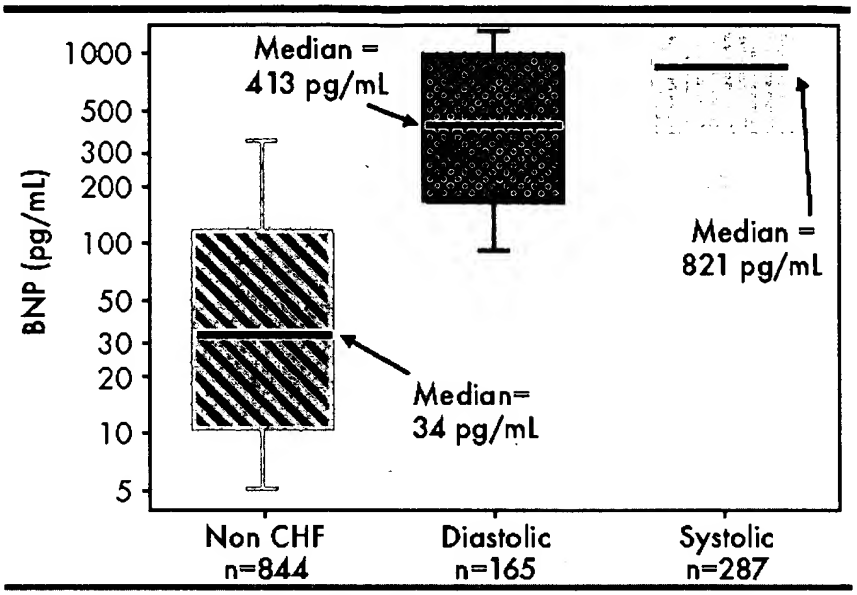

Figure 9. B-type natriuretic peptide (BNP) levels in patients presenting with either systolic or diastolic dysfunction. CHF=congestive heart failure. Reprinted with permission from *J Am Coll Cardiol.* 2003;410(11):2010–2017.[51]

Diastolic Dysfunction. Diastolic dysfunction, which is a common cause of HF in patients presenting with dyspnea, is also associated with high BNP levels.[49,50] In the Breathing Not Properly Study, BNP levels were roughly half as high as for patients with systolic dysfunction (Figure 9).[51] Interestingly, the BNP elevations in diastolic dysfunction were similar in magnitude to those patients with mitral valve restrictive-like filling patterns. A number of studies have elucidated the value of BNP levels to detect diastolic dysfunction. Recently, Lubien et al.[49] assessed BNP levels in 294 patients referred for echocardiography. Patients diagnosed with evidence of abnormal LV diastolic function (n=119) had a mean BNP concentration of 286±31 pg/mL, while the normal LV group (n=175) had a mean BNP concentration of 33±3 pg/mL. Patients with restrictive-like filling patterns on echocardiography had

Consensus Statement 4: Role of BNP in Pulmonary Disease With/Without Associated Cardiac Disease

- **4.1** In approximately 20% of patients with pulmonary disease, BNP will be elevated implying combined HF and lung disease, cor pulmonale, or a misdiagnosis when the true etiology of dyspnea is HF.
- **4.2** In the setting of pulmonary embolism, BNP will be elevated in one third of cases and is associated with right ventricular pressure overload and higher mortality. BNP is not diagnostic for acute pulmonary embolism. A high BNP level in the setting of acute pulmonary embolism is prognostic of a worse outcome, especially when associated with high troponin levels.
- **4.3** The role of BNP levels in chronic pulmonary hypertension remains to be determined. Pulmonary disease which results in pulmonary hypertension and right ventricular pressure or volume overload can lead to elevated BNP levels, usually in the range of 100–500 pg/mL.

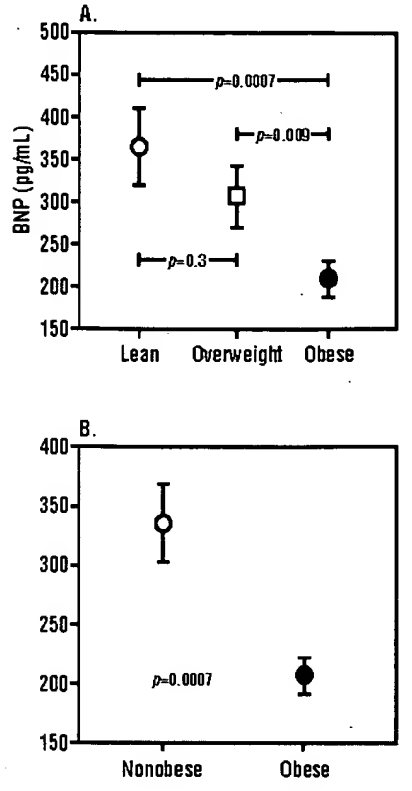

Figure 10. Relationship of B-type natriuretic peptide (BNP) level in lean, overweight, and obese patients. Reprinted with permission from *J Am Coll Cardiol*. 2004;439:1590–1595.[58]

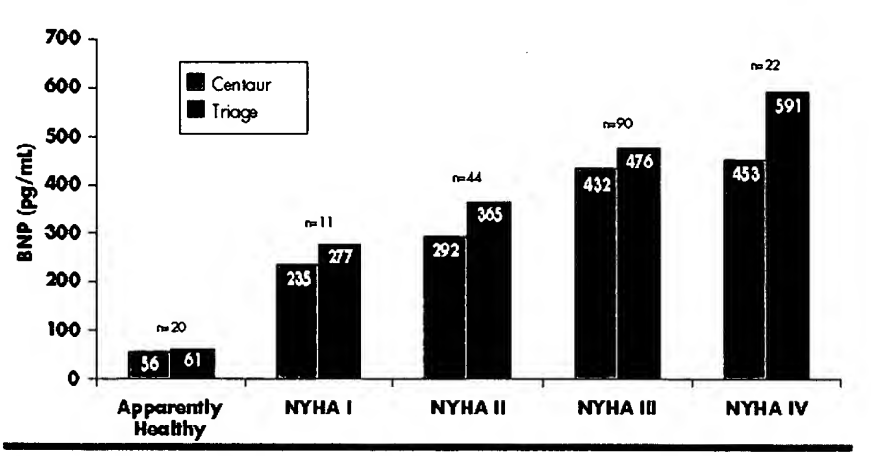

Figure 11. B-type natriuretic peptide (BNP) levels in normal vs. patients with congestive heart failure by New York Heart Association (NYHA) classification. Reprinted with permission from *N Engl J Med*. 2002:347(3);161–167.[35]

the highest BNP levels (408±66 pg/mL), and patients with symptoms had higher BNP levels in all diastolic filling patterns. The area under the ROC curve for BNP to detect any diastolic dysfunction was 0.92 (0.87–0.95; $p<0.001$). A BNP value of 62 pg/mL had a sensitivity of 85%, specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction when systolic function was normal. In the future, therapeutic trials for treating patients with diastolic dysfunction will likely consider including BNP levels as an enrollment criterion and a potential end point for treatment.

Obesity. Obesity is now known to adversely influence systolic and diastolic ventricular function and participate as an important risk factor for the development of CAD and heart failure.[52–55] Physiologically, natriuretic peptides and lipolysis have been closely linked, and adipose tissue is intimately related to the natriuretic clearance receptor.[56,57] This suggests that pathophysiologic mechanisms underlying the relationship between obesity and CVD outcomes could at least partially be related to aberrancies in the natriuretic peptide system, in the clinical realm, the presence of obesity can interfere with the usual diagnostic approach to HF. In particular, signs and symptoms of volume overload can be difficult to ascertain in the obese individual with HF. In such circumstances, establishing the adjunctive diagnostic utility of BNP for the diagnosis of HF is of great importance because of the possibility that obesity might influence the peripheral expression of natriuretic peptides.

Mehra and colleagues[58] first demonstrated that obesity influences the expression of BNP in chronic HF. These investigators found a significant inverse relationship between body mass index (BMI) and BNP levels. These lower levels of BNP in patients with obesity (BMI >30 kg/m^2) were noted despite a similar degree of severity of HF (controlled by functional class, peak aerobic capacity and circulating cytokines) among lean and obese patients (Figure 10). Furthermore, nearly 40% of the obese patients in this study demonstrated BNP levels that were below the threshold of abnormality (<100 pg/mL). Mehra's data are supported by the Breathing Not Properly Study.[59] In this study, patients presenting with HF and low BMI had BNP levels >1000 pg/mL 50% of the time while the obese patients presenting to the ED had BNP levels >1000 pg/mL only 8%–24% of the time. These data have been extended to those obese patients without HF as well as in a recent investigation from the Framingham Heart Study.[60]

Prognosis

BNP in Prognostication and Risk Stratification in Outpatients With HF. Elevations of BNP have been shown to be a powerful marker for prognosis and risk stratification in the setting of HF.[61] In a recent study of 78 patients referred to an HF clinic, BNP showed a significant correlation to the HF survival score.[55] However, it appears that BNP levels are not related to self-reported measures of health status or quality of life, since patients adjust their

Consensus Statement 5: BNP in Diastolic Dysfunction

5.1 BNP may be used to detect patients with diastolic dysfunction. Elevated levels of BNP along with diastolic filling abnormalities might help to reinforce the diagnosis of diastolic dysfunction.

5.2 BNP concentrations above age-adjusted cut-points may identify elderly patients with diastolic dysfunction.

expectations downward as they become more ill.[62] Hence, BNP levels can be supportive of the New York Heart Association (NYHA) functional classification, which is physician assigned, and give complementary information to the symptoms reported by the patient (Figure 11). Harrison et al.[63] followed 325 patients for 6 months after an index visit to the ED for dyspnea (Figure 12). Higher BNP levels were associated with a progressively worse prognosis. The relative risk of 6-month HF admission or death in patients with BNP levels >230 pg/mL was 24 times the risk of levels less than this.

These small, single center studies were validated in a recent analysis of the Valsartan in Heart Failure Trial (Val-HeFT) (Figure 13). Val-HeFT evaluated the role of valsartan in moderate to severe HF, and represents the largest collection of neurohumoral data in HF patients. BNP was measured in all patients at randomization, with follow-up values measured at 4, 12, and 24 months thereafter. Patients with a BNP level above the median had a relative risk of 2.1 for mortality, and 2.2 for first morbid events, in comparison to those with BNP levels below the median. Furthermore, there was an incremental increase in relative risk of mortality and morbidity throughout each quartile (<41 pg/mL, 41–97 pg/mL, 97–238 pg/mL, and >238 pg/mL) of BNP levels. There are several important inferences from this analysis: 1) approximately half of well-treated HF patients had BNP levels <100 pg/mL when measured as outpatients; 2) the lowest quartile of BNP (<41 pg/mL) had the lowest all-cause mortality; 3) the highest quartile (>238 pg/mL) had the highest mortality of 32% at 30 months. Importantly, change from baseline and the percent change of BNP level over a 4- and 12-month period were also evaluated. This analysis demonstrated a direct relationship between percent change from baseline BNP levels and 4-month mortality. Highest mortality was seen in patients with the largest percent increase in BNP, while the lowest mortality was observed in those with the largest percent decrease in BNP.

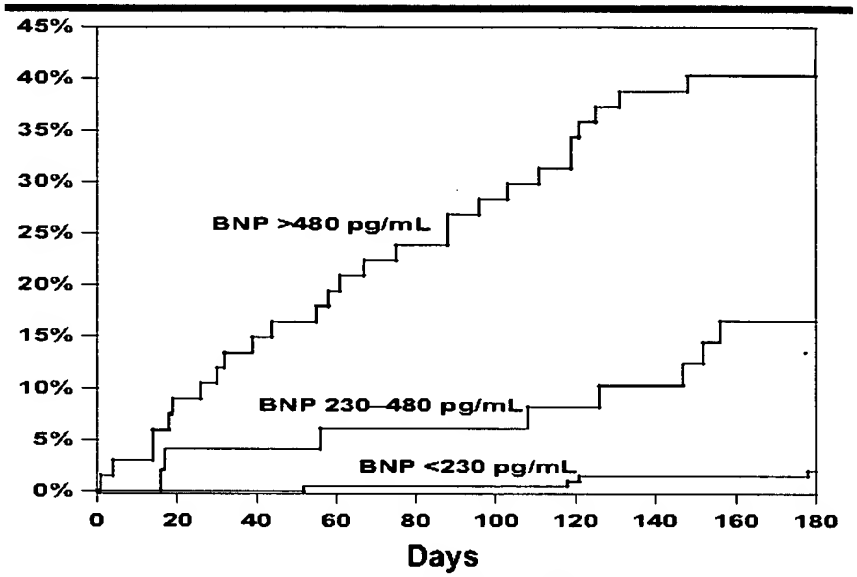

Figure 12. Relationship of B-type natriuretic peptide (BNP) determined in emergency room care to death or heart failure hospitalization. Reprinted with permission from *Ann Emerg Med.* 2002;39:131–138.[63]

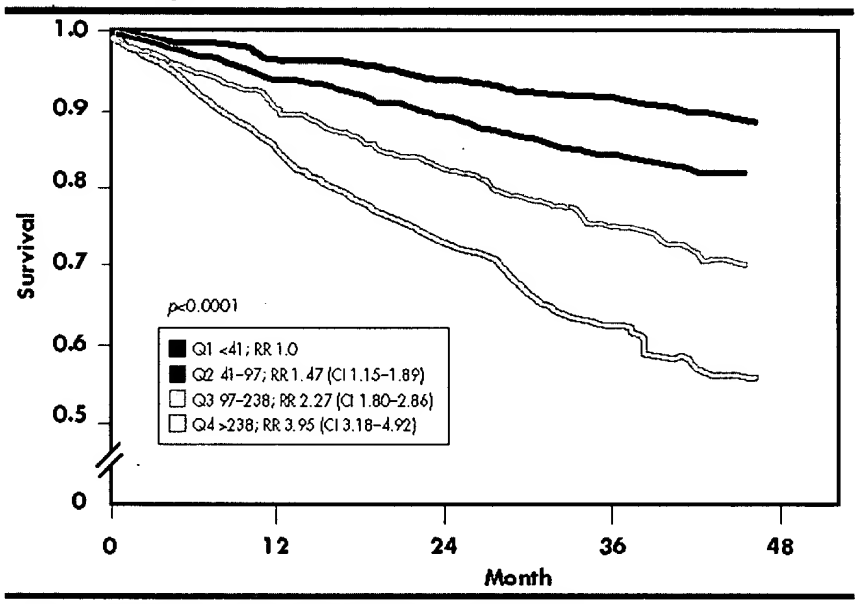

Figure 13. Quartiles of B-type natriuretic peptide (BNP) levels and survival in the Valsartan in Heart Failure Trial (Val-HeFT). RR=relative risk; CI=confidence interval. Adapted with permission from *Circulation.* 2003;107:1278–1283.

BNP Levels and Prognosis in Hospitalized Patients. Several recent trials support the usefulness of changes in BNP levels, as well as predischarge BNP levels, as important markers to optimize the care of patients hospitalized with HF. Bettencourt et al.[64]

Consensus Statement 6: BNP in Obesity

6.1 Since obese patients (body mass index [BMI] >30kg/m²) express lower levels of BNP for any given severity of HF, caution should be exercised in interpreting BNP levels in such patients.

6.2 In obese patients with HF, it is likely that BNP levels followed serially might continue to provide an accurate index of HF stability.

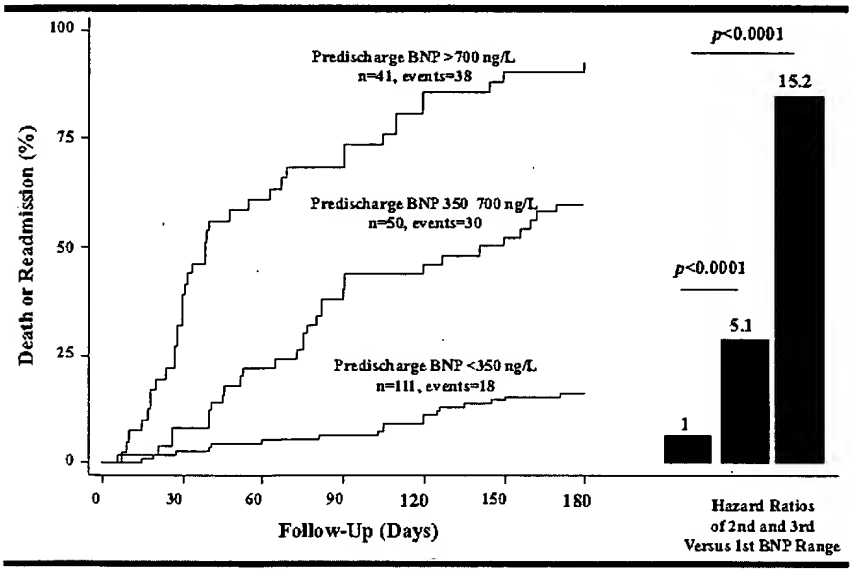

Figure 14. Death or rehospitalization rates according to discharge B-type natriuretic peptide (BNP). Reprinted with permission from *J Am Coll Cardiol.* 2004;43(4):635–641.[66]

investigated the ability of changes in BNP levels during hospitalization to track clinical outcomes in 50 consecutive patients hospitalized with decompensated HF. BNP levels decreased in most patients, but to a significantly greater degree in those who remained free of later readmission for cardiovascular causes and death. Of the seven patients with increases in BNP levels during hospitalization, only one patient was event free at 6 months. Within the subgroup of patients with declining BNP levels during hospitalization, the degree of change in BNP tracked 6-month outcomes. In patients without 6-month hospital readmission or death, BNP levels fell from 619+491 pg/mL to 328+314 pg/mL ($p<0.0001$). In comparison, changes in BNP levels were less pronounced in those who suffered events, with BNP levels decreasing from 779+608 pg/mL to 643+465 pg/mL ($p=0.08$) in this group. Similar results were reported by Cheng et al.[65] in their analysis of 72 patients admitted with decompensated NYHA Class III–IV HF. Of the 72 patients admitted with HF, 22 patients developed 30-day rehospitalization or death. The BNP levels increased by 233 pg/mL in these patients, in comparison to a 215 pg/mL decrease in those who remained free of 30 day adverse events. Finally, Logeart and colleagues[66] demonstrated that HF patients who had a predischarge BNP level >700 ng/L, had an 80% rate of death or hospitalization at 120 days (relative risk=15.2) (Figure 14). Conversely, those with BNP values <350 ng/L had a <10% rate of death or rehospitalization over the same period. In summary, blood BNP levels appear to have powerful prognostic capabilities when measured on admission and on the day of discharge. A favorable pattern for patients is a fall in BNP of >50% from the admission level, or a BNP <350 pg/mL on the day of discharge. Patients with elevations of BNP values during hospitalization, or with values >500 mg/dL on the day of discharge, have high event rates and warrant careful attention for maximizing medical therapy and close follow-up.

BNP and the Prediction of Sudden Cardiac Death. Several studies suggest that BNP, by accurately reflecting acute ventricular filling pressures, dilatation, and stretch, may indicate risk for ventricular arrhythmias and sudden cardiac death. This association was most impressively demonstrated by Berger et al.[67] who, in 452 ambulatory patients with mild to moderate HF (NYHA functional classes I and II) and LV ejection fraction less than 35%, found that BNP levels independently predicted sudden cardiac death. In that study, BNP >130 pg/mL separated patients with high vs. low rates of sudden death. Furthermore, only 1% (1 of 110) of patients with a BNP level <130 pg/mL died suddenly compared with 19% (43 of 227) of patients with BNP levels >130 pg/mL.

Additional evidence that elevated levels of BNP portend ventricular arrhythmias is indirect. Cardiac resynchronization therapy (CRT) is increasingly recognized to improve symptoms and reduce mortality in patients with moderate to severe HF and ventricular asynchrony.[68] Many studies have shown that BNP concentrations fall when CRT therapy is initiated and rise when CRT is subsequently deactivated.[69] Studies have also shown that CRT reduces the incidence of ventricular arrhythmias. Higgins et al.[70] studied 32 patients in whom CRT devices with defibrillator capability were implanted. The study population had a mean age of 65±10 years, 70% had CAD, and all had HF (22% were in NYHA functional class II, 65% in functional class III, and 13% in functional class IV. During a 6-month crossover of CRT-activated to CRT-deactivated therapy, the authors found that patients experienced significantly fewer appropriate device therapies when CRT was activated than when it was not.

Association of BNP With Cardiac Troponin I in HF. There is increasing evidence that myocyte necrosis and apoptosis contribute to progressive LV dysfunction in HF.[71] Several studies have reported elevation of cardiac troponin in patients with decompensated HF in the absence of acute coronary syndrome (ACS) or CAD.[72,73] Recently, Fonarow's group analyzed 251 HF patients referred to the UCLA Cardiomyopathy Center.[74] Troponin I levels were drawn at the time of initial presentation (level of detection 0.04 ng/mL) along with BNP levels. Survival was measured from the date of initial evaluation. The primary end

point was mortality or need for urgent transplantation. Figure 15 shows that in the setting of HF, both troponin I and BNP were independent predictors of survival in HF. The two together gave additive prognostic risk.

Natriuretic Peptide Hormone Measurement in ACS/CAD. Cross-sectional studies have demonstrated statistically significant elevation in natriuretic peptide levels among patients presenting with unstable angina and no evidence of myocardial necrosis.[75,76] When considered in the context of the experimental studies described above, these findings suggest that myocardial ischemia, even in the absence of necrosis, is sufficient to cause release of BNP and NT-proBNP. When compared with patients with HF, however, those with ischemia as the "trigger" for BNP release have more modest elevations of plasma BNP and NT-proBNP, and there is considerable overlap between normal and disease patients. Sensitivity and specificity for BNP will not be adequate to diagnose ischemia because many patients with unstable angina do not have BNP elevation and the levels detected among those with elevation are similar to those seen in other conditions, such as asymptomatic LV dysfunction and pulmonary embolism. In contrast, recent studies demonstrate that BNP or NT-proBNP elevation among patients with unstable angina and non–ST-segment elevation MI is associated with powerful and independent prognostic information.

In 2001, de Lemos et al.[77] measured BNP in 2525 patients with ACS in a substudy of the Orofiban in Patients with Unstable Coronary Syndromes-Thrombolysis in Myocardial Infarction (OPUS-TIMI 16) trial (Figure 16). This was the first large study measuring BNP levels in ACS. Patients were grouped into quartiles based on BNP levels measured approximately 40 hours after the onset of ischemic symptoms. In a linear fashion, increasing levels of BNP were associated with higher 10-month mortality. This association was present across the full spectrum of ACS, including ST-segment elevation MI, non–ST-segment elevation MI, and unstable angina. Further, the association was present among subgroups with no evidence for HF and with no evidence of myocardial necrosis associated with the presenting syndrome.

Another recent publication examined baseline NT-proBNP levels in a multicenter trial evaluating biomarkers in ACS patients. The findings suggest the important prognostic value of biomarkers across the entire spectrum of patients presenting with the ACS.[78]

Sabatine and colleagues[79] performed analyses from OPUS-TIMI 16 and Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction (TACTICS-TIMI) studies using cardiac troponin I, C-reactive protein, and BNP in combination. In multivariate models, each biomarker remained independently associated with adverse cardiac events, demonstrating the unique predictive information that each of these biomarkers provides.

Screening

Screening for Ventricular Dysfunction: The Use of BNP. The success of a population-based screening program for a disease condition is dependent on several factors, including the prevalence of disease; the availability of a good screening test that is acceptable, safe, and inexpensive; proven effective treatment for detected disease; and the availability of, and compliance with, follow-up care of individuals who are detected to have disease.[80]

Given the relatively high diagnostic sensitivity, plasma BNP can be used to rule out LV systolic dysfunction in individuals with "normal" results. However, good diagnostic tests may not be optimal screening tests. In sick, symptomatic patients presenting to a clinician, a test with a high sensitivity is critical because the risk associated with missing a diagnosis is large, but as Freitag and Vasan[81] point out in the screening of asymptomatic patients, a high specificity ("rule in" strategy) is of paramount importance.

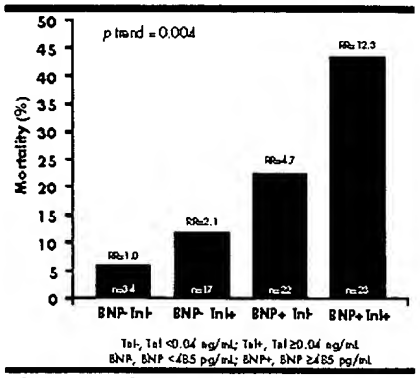

Figure 15. Combination of B-type natriuretic peptide (BNP) and troponin-I (TnI) levels in patients with heart failure.[74]

A study from the MONItoring of Trends and Determinants of CArdiovascular Diseases (MONICA)[82] cohort assessed the utility of BNP in identifying LV dysfunction in 1252 community-based patients aged 25–74 years of age. A plasma BNP concentration of 17.9 pg/mL was found to have a sensitivity of 76% and a specificity of 87% for LV dysfunction as defined by an LV ejection fraction <30%. The overall negative predictive value was 97%, but the positive predictive value was only 16%. In a community-based prospective cohort of 2177 participants from the Framingham study, the performance of BNP for the detection of LV hypertrophy or systolic dysfunction was suboptimal, suggesting limited usefulness of BNP as a mass screening tool. Because of the low prevalence of disease in many of these patient groups and the age- and gender-related changes in BNP levels, screening low-risk populations may not be feasible.

The same investigators, however, examined the long-term prognostic importance of the levels of ANP and BNP in asymptomatic middle-aged persons from the Framingham Offspring Study.[82]

After adjusting for traditional risk factors, Wang and colleagues[83] found that the level of BNP was independently predictive of the risk of death, HF, atrial fibrillation, and stroke over a mean follow-up period of about 5 years. Levels of BNP above the 80th percentile in this cohort (i.e., higher than 20 pg/mL) were associated with an increase by more than 60% in the long-term risk of death. Furthermore, there was a significant

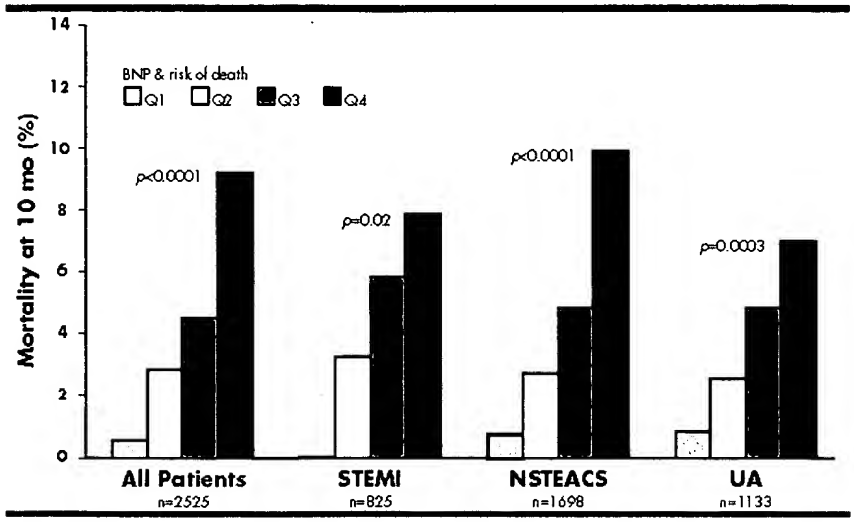

Figure 16. B-type natriuretic peptide (BNP) levels and risk of death in acute coronary syndrome. STEMI=ST-segment elevation myocardial infarction; NSTEACS=non-ST-segment elevation acute coronary syndrome; UA=unstable angina pectoris. Reprinted with permission from *N Engl J Med.* 2001;105:760–1765.

prognostic gradient with respect to the risk of HF, atrial fibrillation, and stroke among the three levels of BNP (low, intermediate, and high) examined. This remarkable finding suggests that in the asymptomatic community-based cohort, there are important prognostic data even in the range of BNP levels <100 pg/mL, the level used to rule out HF in 90% of acutely dyspneic patients.

Screening in the Higher-Risk Populations. Silver and Pisano[84] using traditional cut-points, found a high incidence of elevated BNP levels in an unselected at-risk population in a community-based setting. This, along with other emerging evidence, suggests that BNP may additionally serve as an important screening tool to detect patients progressing from Stage A to Stage B in the HF natural history pathway. This suggests that using lower cut-points of BNP along with other historical, clinical, and laboratory information is likely to lead to more appropriate evaluation and triage of these patients.

In the population-based Hillingdon HF Study,[85] one third of patients referred to a rapid-access clinic by a primary care physician with a new diagnosis of HF had the diagnosis confirmed on further assessment. The diagnostic value of the plasma BNP concentration compared with the clinical opinion of an expert panel was very high. The area under the ROC curve for plasma BNP was 0.96, compared with 0.79 for cardiothoracic ratio. Taking a cutoff value of 22 pmol/L (76.4 pg/mL) combined a very high negative predictive value (98%) with an acceptable positive predictive value of 70%, a sensitivity of 97%, and specificity of 84%. Therefore, this study suggests there is a potential for the BNP test to improve the efficiency of referring patients for further assessment.

Epshteyn et al.[86] found that in a high-risk but asymptomatic diabetic population, a BNP cut-point of about 40 pg/mL could detect underlying systolic and diastolic dysfunction. Atisha et al.[87] found only rare and mild cases of cardiac dysfunction (mainly diastolic) in patients undergoing echocardiography whose BNP levels were <20 pg/mL. Recently, Heidenreich et al.[88] found that screening patients with BNP using a cutoff of 24 pg/mL followed by echocardiography was economically attractive for 60-year-old men and possibly for women for patient groups with at least a 1% prevalence of moderate or greater LV systolic dysfunction (ejection fraction <40%). Screening all patients with echocardiography was expensive, but sequential BNP-echocardiography screening strategy was economically attractive.

Consensus Statement 7: BNP Measurement in Sudden Death, Acute Coronary Syndrome, and Coronary Artery Disease

7.1 BNP is a significant independent predictor of mortality in HF. Changes in BNP over time are associated with morbidity and mortality. This provides physicians with an opportunity to provide more aggressive treatment to these patients.

- **7.1.1** Several studies suggest that BNP levels are predictive of sudden cardiac death. Thus, BNP levels might help us further stratify patients who might most benefit from newer therapies, such as implantable cardiac defibrillators.
- **7.1.2** Additional biomarkers (troponin, and C-reactive protein) may provide unique, adjunctive, and independent information to a BNP measurement with regard to patient outcomes.
- **7.1.3** When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Such information is likely to enhance our ability to appropriately triage higher-risk HF patients and more reliably identify low-risk HF patients who may be candidates for less intensive evaluation and therapy.
- **7.1.4** In the setting of ACSs, low-level troponin elevation is highly predictive of recurrent ischemic events, whereas BNP appears to be a "pump failure" marker, more closely associated with death and HF progression. Using these two markers together improves the detection of patients at risk for adverse events.
- **7.1.5** In the future, BNP will likely be included in multi-marker panels that include troponin and C-reactive protein, as each of these markers provides unique and independent information with regard to patient outcomes.

7.2 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Multi-marker panels that include BNP, troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes.

Treatment Monitoring

BNP Levels in the Hospitalized Patient. There are approximately 1 million admissions annually to US hospitals for HF.[89] While patients who are admitted to the hospital with decompensated HF often have improvement in symptoms with the various treatment modalities available, there has been no good way to evaluate the long-term effects of the short-term treatment. Readmission after hospitalization for HF is surprisingly common, estimated at 44% at 6 months within the Medicare population.[90] Considering that hospitalization is the principal component of the cost for patient care (70%–75% of the total direct costs),[91] a reduction in HF hospitalizations is an appropriate goal for whatever treatment modalities are in place.

Though not yet an FDA-approved indication, the use of BNP for targeting treatment of patients with HF is under active investigation. Targeting treatment of disease has precedent—treatment of hypertension is targeted to BP, diabetes to blood sugar, and hypercholesterolemia to cholesterol levels. The fact that BNP has a short half-life, has easy-to-measure levels, and is a surrogate for wedge pressure, volume, NYHA functional class, and prognosis suggests its usefulness as a guide to therapy in HF.

Does High BNP Always Mean High Filling Pressure? Since a major stimulus for the release of BNP is increased wall tension, one might expect that BNP levels would correlate with elevated LV filling pressures. Indeed, there is a body of data[92] to support that supposition. However, in the clinical setting there are many occasions where high BNP level is not associated with high filling pressures. Some of these situations include BNP elevations from right-sided failure secondary to cor pulmonale, pulmonary embolism, or primary pulmonary hypertension; acute or chronic renal failure; and rapid lowering of the wedge pressure with diuretics and/or vasodilators before a Swan-Ganz catheter is placed. Additionally, under some circumstances, BNP levels might be normal when the wedge pressure is high. This would most likely occur in acute mitral regurgitation where the increase in capillary pressure is upstream from the left ventricle and in "flash" pulmonary edema, where the BNP might not have had time to be synthesized.

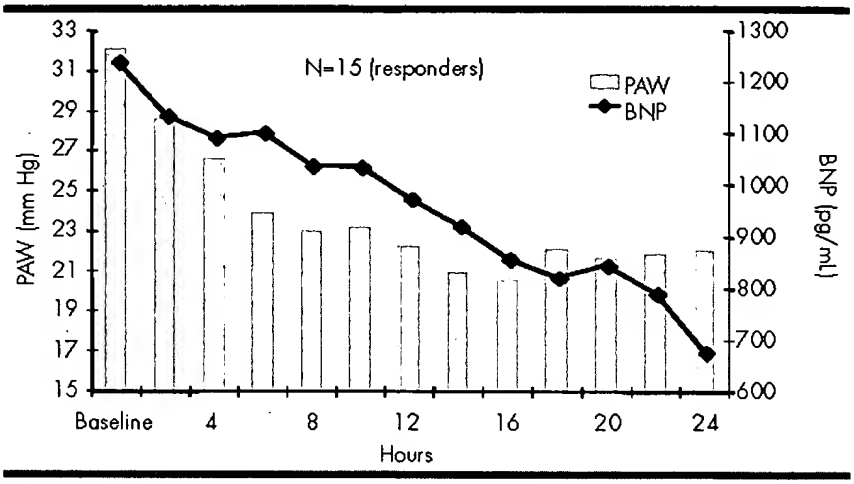

Figure 17. Relationship of B-type natriuretic peptide (BNP) levels and pulmonary artery wedge (PAW) pressure in patients with volume-overloaded congestive heart failure. Reprinted from *Journal of Cardiac Failure*, 7, Kazanegra R, Cheng V, Garcia A, et al., A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study, 21–29, Copyright 2001, with permission from Elsevier.

This would most likely occur in acute mitral regurgitation where the increase in capillary pressure is proximal to the left ventricle and in "flash" pulmonary edema, where the BNP might not have had time to be synthesized due to the short time from symptom onset.

In a given patient the BNP level does not always correlate to wedge pressure. However, in a patient admitted with HF and high filling pressures secondary to volume overload, along with a high BNP level ("wet BNP," see below), a treatment-induced decrease in wedge pressure will almost always be associated with a rapid drop in BNP level, as long as the patient is maintaining adequate urine output. Kazanegra et al.[93] measured wedge pressure, hemodynamic measurements (pulmonary capillary wedge pressure [PCWP], cardiac output, right atrial pressure, systemic vascular resistance), and BNP levels every 2–4 hours for the first 24 hours and every 4 hours for the next 24–48 hours in patients admitted for decompensated HF. PCWP dropped from 33 ± 2 mm Hg to 25 ± 2 mm Hg over the first 24 hours, while BNP dropped from 1472 ± 156 pg/mL to 670 ± 109 pg/mL (Figure 17). The correlation between BNP levels and other indices of cardiac function–cardiac output (thermodilution), mixed venous oxygen saturation, and systemic vascular resistance was nonsignificant. It should be emphasized that patients with end-stage HF admitted for transplant workup who are not acutely volume overloaded may not demonstrate a decline in BNP levels as the wedge pressure is lowered ("dry BNP").

Consensus Statement 8: BNP Screening in Higher-Risk Populations

8.1 At this time, BNP testing is not appropriate for screening asymptomatic, low-risk populations for LV systolic dysfunction.

8.2 There may be some value in using plasma BNP to screen high-risk subgroups of the population such as post-MI patients, diabetic patients, or those with an extended history of uncontrolled hypertension. It is important to note that echocardiography is likely to remain the main method of assessing LV function in this setting.

Compensated and Decompensated BNP Levels. The BNP level of a patient who is admitted with decompensated HF is comprised of two components: that of a baseline, compensated, "dry" BNP level and that occurring from acute pressure or volume overload (decompensated or "wet" BNP level). At the point of decompensation, a patient's BNP level will be a sum of their baseline BNP level plus what volume overload adds a sum of baseline BNP plus the additional production of BNP from ventricular stress due to acute volume overload.

The lower the discharge "dry weight" or compensated BNP level is, the less likely that the patient will be an early victim to rehospitalization. This is because a low BNP level (<200–300 pg/mL) represents an NYHA functional class II patient and one that is more likely to be in a true euvolemic state. Knowing a patient's baseline compensated or "dry weight" BNP level is likely to be important in monitoring the patient in the first 30 days after discharge. Early elevations of BNP over baseline soon after discharge may trigger the need for more intensive outpatient surveillance and therapy.

Stevenson[94] has published a rapid assessment of hemodynamic status to stratify patients to treatment to diuretics, vasodilators, or inotropic agents. Patients who are admitted to the hospital with either new-onset or decompensated HF are usually volume overloaded. Treatment in this setting includes diuretics and vasodilators when patients are "wet and warm." In general, almost all these patients have BNP levels >600 pg/mL. In fact, if BNP levels were less than this, one should carefully consider other methods to ascertain a patient's volume status and/or caveats to BNP interpretation (see above).

Diuretics, inotropes, and vasopressors are often indicated when patients are classified as "wet and cold." These patients frequently have BNP levels >1000 pg/mL. Patients that are "cold and dry" have BNP elevations secondary to systolic dysfunction, but perhaps BNP levels are not as high as the "cold and wet" patients. Finally, patients who are "warm and dry" are likely to have lesser elevations of BNP levels.

Pitfalls and Caveats in BNP Interpretations. There are circumstances whereby plasma BNP levels may be affected by ambient biological conditions or disease unrelated to HF. Plasma BNP tends to be higher in the elderly, in women, in renal insufficiency, immediately following exercise, and after open heart surgery. There are mixed reports of altered BNP levels with atrial fibrillation and thyroid disease, but it can be increased in hyper- and hypothyroidism, and in some patients with atrial fibrillation. More research is necessary.

Plasma BNP can be evaluated in patients with acute, life-threatening illness such as sepsis and toxemia of pregnancy. The mechanism of these alterations in plasma BNP in these patients is not clear, but heightened BNP may not be due to "congestive HF."

Low plasma BNP levels have been reported in patients with stable, ambulatory HF.[94] In a subset of patients with symptomatic but stable HF due to dilated cardiomyopathy, plasma BNP levels were found to be below what would be considered "normal" (<100 pg/mL). The BNP test cannot replace or supersede the judgment of the clinician, as the diagnosis of HF requires clinical evaluation. The importance of the context in which BNP is measured cannot be overstated. A normal plasma BNP in a patient presenting to the ED with dyspnea has more negative predictive power than a "normal" plasma BNP in a patient with stable, chronic HF.

How Often Should One Obtain a BNP Level in the Hospital? This is an often-asked question with no single right answer. Certainly, as one becomes more experienced in using BNP levels in the hospital, one will likely tailor requests for blood draws at admission and discharge and after any major clinical change, either for better or for worse. One author (ASM) obtains a BNP level after 24 hours of treatment. Failure of BNP levels to fall in a 24-hour period may delineate a high-risk patient who should receive more vigorous treatment. If a very sick patient is being treated in the intensive care unit without Swan-Ganz guidance, perhaps more frequent assessment of BNP levels (every 4–6 hours) is warranted. During nesiritide infusion, BNP levels do not need to be measured (measure would be sum of endogenous plus exogenous). However, exogenous BNP should be cleared within 2 hours following infusion. Since the half-life is 22 minutes, 4 half-lives will then represent the new steady state and one will have reached 96% of the change in levels by this time. Delay in analysis beyond this time frame will only provide changes that are smaller than the coefficient of variation of the assay.

What if a BNP Level Does Not Fall During Hospitalization? There may be several explanations why elevated BNP levels do not fall with treatment in some patients with HF. First and foremost, the high BNP level may actually be the patient's "dry" BNP level and will not be acutely lowered with diuretics or vasodilators. These patients tend to be NYHA functional class IV and have a poor prognosis.

Secondly, a consideration of the differential diagnosis must be entertained. Patients at their hemodynamically dry weight with a BNP of 700 pg/mL, but with a new superimposed pulmonary embolus, may demonstrate severe dyspnea and no response to HF therapy.

Perhaps patients who have high BNP levels that do not respond to treatment should be considered for other more invasive types of therapies such as cardiac transplantation or use of ventricular assist devices. Patients with a wide QRS might be considered for biventricular pacing. In a recent trial of patients who received ventricular assist devices for end-stage HF, BNP levels appeared to fall as remodeling of the heart occurred, and an early decrease in BNP plasma concentration was indicative of recovery of cardiac function during mechanical circulatory support.[95] In any event, patients with high BNP levels at discharge are at increased risk, and if nothing else, are candidates for early follow-up and perhaps home nursing visits.

There are other reasons that a BNP level might not fall with treatment. It is possible that with parenteral diuretic treatment of the decompensated, prerenal patient, further azotemia might occur. This will likely down-regulate BNP clearance receptors, and BNP levels will rise. In this setting, nesiritide infusions might be indicated. Another possible scenario is that a patient with left and right HF and significant ascites and/or edema, may often diurese many liters before BNP levels actually drop. This is possibly because rather than lowering wedge pressure, the urine output is occurring secondary to mobilization of third space fluid. Continuing diuresis and/or vasodilatation should eventually lower BNP levels. Finally, acute, severe pressure or volume overload might turn on the transcription of the mRNA for BNP to such a degree, that even upon initial lowering of the wedge pressure, BNP levels might still be increasing.

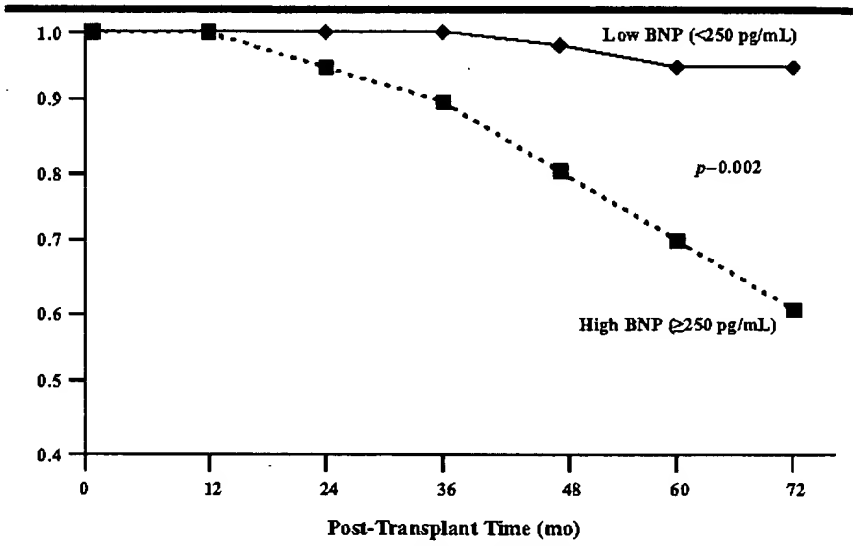

Figure 18. Kaplan Meier survival plot for low and elevated BNP levels indicating poor survival (cardiac deaths) of heart transplant recipients with an elevated BNP. Reprinted with permission from *Am J Cardiol.* 2004;94(4):454–458.[103]

BNP and Heart Transplantation. Since BNP reflects ventricular wall stress and pressure, levels of this hormone in heart transplant recipients have been studied as a candidate marker of allograft function. Early case-controlled studies in heart transplantation suggested that stable recipients demonstrated elevated BNP levels.[96-99] Buckley et al.[97] hypothesized that the difference in baseline BNP levels between the controls and transplant recipients could be attributed to higher systemic BP, older age, and decreased renal function of the transplanted cohort. Ationu et al.[98] examined the ventricular expression of BNP by evaluating endomyocardial biopsy specimens and demonstrated a linear relationship between plasma and ventricular BNP levels ($r=0.8$, $p<0.05$), thus finding that elevated levels of BNP are detectable in the RV myocardium of the transplanted heart. The same group also demonstrated elevated BNP gene expression at the mRNA level compared with control subjects.[100] To negate any effects from cardiac surgery per se for causing the difference in the BNP level, Geny et al.[101] utilized post-bypass patients as controls and reported the same findings as previous investigators, confirming that the elevated BNP level found among transplant recipients is not related to the surgery but to physiological changes in the transplanted heart. Park et al.[96] analyzed 237 consecutive BNP levels in 87 stable adult heart transplant recipients, representing the largest study to date. While mean BNP level among the cohort was 258±276 pg/mL, the median value was significantly lower (153 pg/mL). These findings suggest a three- to four-fold elevation in "stable" cardiac allograft recipients and demonstrate that despite an observed normal systolic performance, the transplanted heart persistently manifests restrictive or relaxation abnormalities[102] resulting from the process of engraftment and ongoing effects of rejection (insidious or overt), hypertension or RV aberrations. Mehra et al.[103] studied the prognostic utility of BNP measurements in the late phase after heart transplantation. In this study, Mehra and colleagues found that a BNP level >250 pg/mL in chronic survivors is closely related with allograft failure; the development of CAD; and pointed to an increased likelihood of cardiac death (Figure 18).

Therapy/Administration as a Therapeutic Agent

B-Type Natriuretic Peptide as a Therapeutic Agent for Decompensated HF. In addition to being a suitable marker of CVD that bears both diagnostic and prognostic importance in HF, B-type natriuretic peptide is a rational therapeutic option again because of its primordial homeostatic functions. [*For the sake of clarity, the therapeutic applications of BNP will be denoted as B-type natriuretic peptide.*]

Consensus Statement 9: What if a BNP Level Does Not Fall With Hospitalization?

9.1 While in a given patient the BNP level does not always correlate to wedge pressure, in a patient admitted with HF and high filling pressures secondary to volume overload, along with a high BNP level (decompensated or "wet BNP"), a treatment-induced decrease in wedge pressure will almost always be associated with a rapid drop in BNP levels, as long as the patient is maintaining adequate urine output.

9.2 BNP levels do not need to be drawn every day a patient is in the hospital. Rational use of BNP levels would be on admission, after a major treatment effect (usually after 24 hours of treatment), and when discharge is contemplated (and euvolemia reached).

9.3 Failure of BNP levels to decrease during hospitalization is a poor prognostic sign, suggesting consideration of more intensive monitoring, treatments and follow-up.

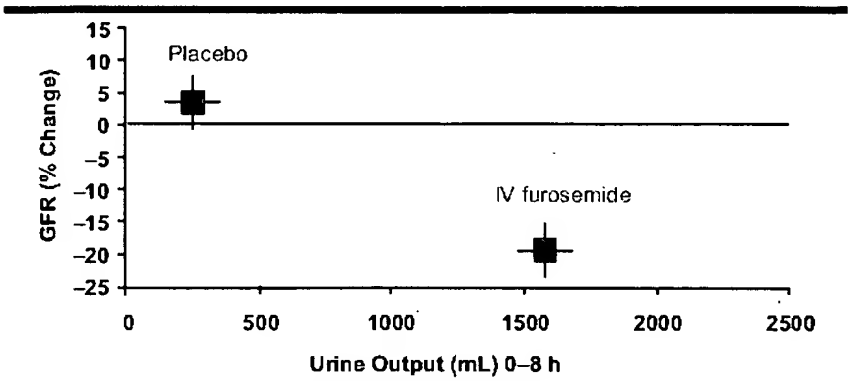

Figure 19. Furosemide monotherapy causes significant decline in glomerular filtration rate (GFR). Change in GFR after IV furosemide 80 mg in HF. Reprinted with permission from *Circulation*. 2002;105:1348–1353.[119]

The pleuripotent effects of B-type natriuretic peptide, including vasodilatory, natriuretic, diuretic, antifibrotic and lusitropic properties, make it an especially attractive option in the management of acute decompensated HF (ADHF).[104,105] The adjunctive ability of B-type natriuretic peptide to inhibit the renin angiotensin system, inhibit the release of aldosterone, block the effects of endothelin, and promote central sympatho-inhibitory tone, adds further to its salutary properties.[106]

HF is an insidious clinical syndrome that is initiated by overt cardiac injury either acute (MI) or chronic (e.g., hypertension), but perpetuated by ongoing neurohormonal activation. The initial benefit of stimulation of the RAAS and the sympathetic nervous system is to preserve blood flow to critical organs and support systemic BP through vasoconstriction and salt and water retention. Angiotensin II is a vasoconstrictor and growth-promoting neurohormone. It promotes increased sodium reabsorption in the proximal tubule. Angiotensin II also stimulates the production of tumor necrosis factor-α and transforming growth factor β-1—both of these cytokines lead to enhanced growth stimuli for cardiac myocytes.[107] Norepinephrine provokes vasoconstriction and is especially toxic to the myocardial cell. The protean role of aldosterone is becoming increasingly apparent.[108–110]

In addition to promoting sodium reabsorption from the distal collecting tubule, it is now evident that aldosterone leads to collagen matrix turnover, promotes cellular inflammation, and potentiates the effects of catecholamines. Endothelin-1 is perhaps the most potent vasoconstrictor yet described. Endothelin-1 increases cardiac afterload, decreases glomerular filtration rate,[111] and stimulates myocyte hypertrophy. It has been demonstrated in an incontrovertible manner that the extent of neurohormonal derangement parallels the severity of underlying LV dysfunction and HF. It is also apparent that angiotensin II, norepinephrine, aldosterone, and endothelin are all associated with direct myocardial toxicity, and among other effects, stimulate fibrosis, remodeling, and generate ventricular arrhythmias. When this process proceeds in an unabated manner, LV dysfunction progresses and worsening HF ensues.

The discovery of a natriuretic effect of atrial tissue extracts by de Bold[112] in 1981 has led way to discovery of the countervailing properties of the natriuretic peptide system and its therapeutic potential. Remarkably, there is evidence that B-type natriuretic peptides exert a counterbalancing influence on many of the foregoing deleterious consequences of neurohormonal activation.

B-type natriuretic peptide binds to a family of natriuretic peptide receptors located on endothelial and smooth muscle cells, specifically NPR-A, NPR-B and NPR-C (Figure 3b). The function of NPR-C is largely as a clearance receptor. The physiological properties of B-type natriuretic peptide are thus mediated by both NPR-A and NPR-B. The union of B-type natriuretic peptide to NPR-A and NPR-B results in the generation of 3′ 5′-cGMP. cGMP is felt to be the second messenger through which the favorable properties of B-type natriuretic peptide occur.[113,114] In the kidney, B-type natriuretic peptides increase glomerular filtration and inhibit sodium reabsorption leading to a natriuresis and diuresis.[115] In addition, B-type natriuretic peptide inhibits renin secretion and directly inhibits the release of aldosterone from adrenal cortical cells. In the periphery, B-type natriuretic peptide relaxes smooth muscle causing vasodilation.[116,117] At the heart, B-type natriuretic peptide improves coronary blood flow[118] and exerts a lusitropic effect on the left ventricle. This favorable cascade of effects of B-type natriuretic peptide appears to be overwhelmed in HF either because of the extent of pathobiological neurohormonal activation, enhanced clearance of B-type natriuretic peptide, abnormal protein synthesis, or reduced receptor affinity. As such, efforts to up-regulate the effects of B-type natriuretic peptide have been pursued with a focus on the exogenous administration of B-type natriuretic peptide (a.k.a. nesiritide [Natrecor] Scios Inc., Fremont, CA).

The ideal candidate drug for ADHF ought to be one that improves the deranged hemodynamics in ADHF, promotes a diuresis, has minimal effect on myocardial oxygen consumption, does not possess inotropic activity, is not proarrhythmic, and does not contribute to further neurohormonal activation or additional ventricular remodeling.

Current Therapies for ADHF. *Diuretics* are clearly beneficial in the setting of ADHF as they quickly and effectively lower filling pressures. However, an emerging database is now demonstrating very worrisome consequences of excessive diuretic exposure. Diuretics lead to contraction of effective arterial blood volume, which is a further stimulus for renin production and subsequent angiotensin II production. The usual flux in electrolytes is also problematic as it engenders ventricular rhythm disturbances, some of which may on

occasion be quite serious. Remarkably, there have been no data demonstrating a survival advantage when diuretics are used for ADHF but they remain the "gold standard" therapy. Data are now emerging that diuretics drop renal blood flow and reduce GFR (Figure 19).[119] Preliminary data from the Acute Decompensated Heart Failure National Registry (ADHERE)[120] database have in a very provocative way suggested that significant diuretic use, especially in the setting of renal insufficiency, imparts a negative risk on survival for patients admitted with ADHF. It is advised that diuretics remain in the core treatment strategy for ADHF but judicious use ought to be considered and attention given to treatments that will minimize the need for diuretics.

60-Day Follow-Up	Milrinone (n=477)	Control (n=472)
Days until discharge	5.7 ± 13	5.9 ± 13
Adverse events	12.6%*	2.1%
Sustained hypotension	10.7%*	3.2%
Acute MI	1.5%	0.4%
Rehospitalization or death	35.0%	35.3%
Death	10.3%	8.9%

Figure 20. Milrinone in Outcomes of a Prospective Trial of Intervention Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). Forty-eight hour infusion of milrinone (0.5 ng/min) within 48 hours of admission for worsening of heart failure. MI=myocardial infarction; *$p<0.05$. Reprinted with permission from JAMA. 2002;287:1541–1547.[122]

Inotropes represent a complex treatment option. Whether catechol or non-catechol in origin, inotropes and inodilators stimulate cardiac output by upregulating cellular levels of cyclic adenosine monophosphate. Even though the increase in cardiac output is beneficial in the short term, the subsequent injury to the myocardium and the risk of serious arrhythmias mitigates against indiscriminate use of inotropes and inodilators.[121] The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic HF, (OPTIME) randomized 800 patients presenting with ADHF, but not in shock, to milrinone vs. placebo with background standard therapy. Milrinone was given in standard concentrations akin to its use in most medical centers. Patients receiving placebo plus standard therapy realized fewer episodes of hypotension, fewer arrhythmias, significantly fewer episodes of atrial fibrillation and a trend toward better survival (Figure 20).[122] In a previous trial, which evaluated the potential benefit of prostacyclin in HF, a substantial number of patients received dobutamine. The short-term mortality results for those patients receiving dobutamine were quite negative. This is further supported by the adverse 6-month mortality data for patients randomized to dobutamine in the Levosimendan Infusion vs. Dobutamine (LIDO), trial,[123] which evaluated the calcium sensitizer levosimendan as therapy for ADHF. Dobutamine infusions have been shown to significantly increase aldosterone levels while other catechols have been associated with striking increases in plasma renin activity.[124,125] Thus, the inotropes do not represent a viable option for patients presenting with ADHF unless shock or impending shock with evidence of a low cardiac output is a significant feature of the presenting illness.[126]

IV nitroglycerin and nitroprusside are widely accepted as appropriate therapies for ADHF and clearly do provide transient hemodynamic improvement. Parenteral nitroglycerin is a potent peripheral and coronary vasodilator. Its greatest effect is on preload. Acute administration drops cardiac filling pressures. Sustained benefit from nitroglycerin is lacking, however, due to the rapid onset of nitrate tolerance. This greatly curtails its efficacy in the setting of ADHF.[127,128]

Sodium nitroprusside is a balanced arterial and venodilator that drops afterload acutely and results in a reflex improvement in cardiac output. Heart rate increases with nitroprusside administration. Cyanide toxicity is an especially worrisome adverse consequence of nitroprusside use and in most facilities, the use of nitroprusside requires an intensive care unit setting, and not

Consensus Statement 10: B-Type Natriuretic Peptide as a Therapeutic Agent for Decompensated HF

10.1 The patient with ADHF has advanced disease notable for neurohormonal activation, ventricular remodeling and risk of further decompensation.

10.2 The current armamentarium of therapies and their administration for patients with ADHF have significant risks associated with their potential benefits.

10.3 IV administration of recombinant B-type natriuretic peptide (nesiritide) as a therapeutic agent has been demonstrated to maximize the risk/benefit ratio of therapies for ADHF. These benefits include hemodynamic and reverse remodeling effects while the risk of inotropy and proarrhythmia are obviated.

10.4 Because of the efficacy and utility of recombinant B-type natriuretic peptide (nesiritide) in clinical trials for patients with ADHF who are hospitalized, early data and additional trials of strategies which employ recombinant B-type natriuretic peptide (nesiritide) in either the out-patient setting or ED are currently underway.

10.5 Because of the unique homeostatic and remodeling properties of recombinant B-type natriuretic peptide (nesiritide), this therapy is also being evaluated for its role in settings such as post-MI and post-cardiac surgery.

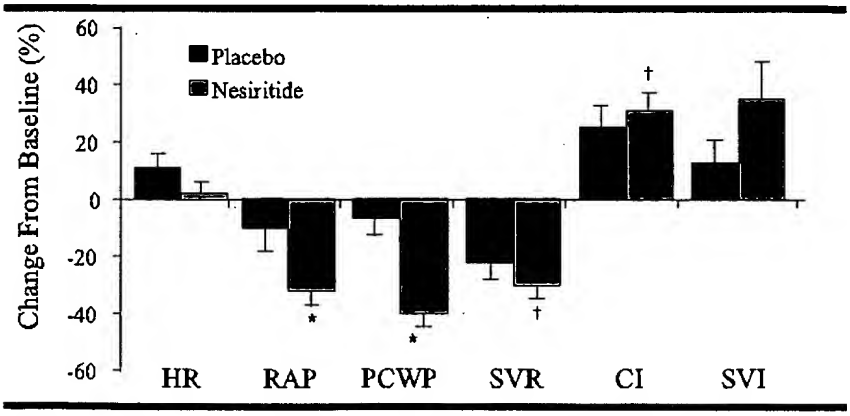

Figure 21. Hemodynamic effects of nestritide in heart failure patients. Sixteen patients received a 4-hour continuous infusion of human brain natriuretic peptide (0.025 and 0.05 μg/kg/min) or placebo. HR=heart rate; RAP=right arterial pressure; PCWP=pulmonary capillary wedge pressure; SVR=systemic vascular resistance; CI=cardiac index; SVI=stroke volume index; *$p<0.01$ vs. placebo; †$p<0.05$ vs. placebo. Reprinted with permission from *J Card Fail.* 1998;4:37–44.[115]

infrequently, an indwelling arterial line is required as well. Once again, evidence-based data attesting to a survival advantage of these compounds in the setting of ADHF are lacking. Tolerance and headache are problems with parenteral nitroglycerin while toxicity, especially in the setting of renal or hepatic disease, is an ever-present risk for nitroprusside. Both agents lead to further augmentation of the neurohormonal cascade due to their vasodilatory properties and corresponding increases in heart rate. The acute administration of sodium nitroprusside has been associated with a greater than four-fold increase in plasma renin activity and a two-fold increase in norepinephrine levels.[129] The activation of the neurohormonal cascade is less acute with parenteral nitroglycerin but has been described. Thus, these compounds with albeit favorable hemodynamic profiles do not fully address the problems in ADHF and carry with them worrisome side effects and consequences.

The foregoing data would suggest that current treatment options for ADHF have been less than ideal—which is perhaps the main reason for a lack of consensus on management of ADHF. There remain no evidence-based guidelines to referee the acute management of patients with ADHF and the clinician must resort to reasoned clinical intuition in the construct of an effective treatment strategy for ADHF.

The complexity of the patient with ADHF is in part the reason why comprehensive guidelines have not yet been constructed. Data emanating from ADHERE have been quite revealing. The mean age of the patient admitted with ADHF is 75; nearly 50% are female and LV function is >40% in nearly half of all cases. Significant comorbidities are commonly seen, including CKD, diabetes, and atrial fibrillation. Outcomes are much less good than had been previously presumed. The risk of death during an admission for ADHF is 4% but this varies from ≈2% to >20% depending on the absence or presence of identified risk factors.[130] Re-hospitalization is yet another concern with a 2% rate at 3 days, 10% at 30 days, and a 50% readmission rate at 180 days. Given the overwhelming number of annual HF admissions, now nearly 1 million, these less than ideal outcomes are especially worrisome. Clearly, better therapeutic approaches are needed.

Natriuretic Peptides as Therapy for ADHF. Natriuretic peptides represent a significant opportunity to reduce the morbidity of ADHF and are much closer to ideal drugs for this condition than other currently available agents.

Hemodynamic Effects of Natriuretic Peptides. The administration of natriuretic peptides is associated with a reduction in pulmonary capillary filling pressures, a decrease in pulmonary vascular resistance, a drop in central venous pressures, reductions in systemic BP, and a reflex increase in cardiac output due to the unloading effect of vasodilatation.[131] What is, however, more remarkable is the lack of a reflex tachycardia, a finding consistent with the sympathoinhibitory function of natriuretic peptides (Figure 21). Moreover, the reduction in preload and afterload without an increase in heart rate would be consistent with a decrease in myocardial oxygen consumption and a decrease in ventricular stress—a stimulus that is presumed to drive the neurohormonal activation attributed to ADHF. It is also noted that tolerance to these effects has not been demonstrated, thus, these favorable changes in hemodynamics are present and persistent throughout administration of the natriuretic peptides.

Absence of Inotropic and Proarrhythmic Effects of Natriuretic Peptides. Classic strain-gauge physiological evaluations have clearly demonstrated that human trabeculated cardiac muscle fails to generate force-derived tension at any level of natriuretic peptide administration (Figure 22).[132] These data plus the observed lack of reflex tachycardia support a complete absence of inotropic potential for the natriuretic peptides. The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) demonstrated that dobutamine increased heart rate and ventricular ectopy in a statistically significant manner compared with nesiritide. By two common criteria of pro-arrhythmia, dobutamine led to worrisome ventricular arrhythmias while nesiritide did not (Figure 23).[133,134] More recent data have tested the effects of B-type natriuretic peptide vs. dobutamine in patients with ADHF of ischemic etiology. There was no increase in ventricular tachycardia, couplets, repetitive beats, or resting heart rate in patients treated with nesiritide but dobutamine led to striking increases in all parameters. In fact, ventricular ectopy was *decreased* compared

with baseline in those patients treated with nesiritide.[135]

Reverse Remodeling Effects of Natriuretic Peptides. Another homeostatic attribute of B-type natriuretic peptide is the ability to restore the cardiac structure (myocyte and extracellular matrix) back toward its native state. This is perhaps the most intriguing potential benefit of the therapeutic use of natriuretic peptides. Animals devoid of NPRs demonstrate an aggressive hypertrophic response of the myocardium notable for extensive areas of fibrosis, and animals that are bred with the inability to produce B-type natriuetic peptide, demonstrate exaggerated growth responses to hemodynamic stress.[136] Further, the inhibition of aldosterone and endothelin-1 contributes to a reduction in the remodeling cascade. CNP is felt to act in the central nervous system to provoke the sympathoinhibitory responses noted but may also have an anti-fibrotic role as well.[137]

Clinical Trials/Investigations Using Natriuretic Peptides as a Therapeutic Option for ADHF. The foregoing discussion sets the stage for the use of B-type natriuretic peptides as therapy for ADHF. To date, the only available iteration of B-type natriuretic peptide is nesiritide.

Colucci et al.[138] initially reported on the use of IV nesiritide as treatment of decompensated HF. Two trials were completed—the efficacy trial and the comparator trial. Patients presenting with ADHF underwent right heart catheterization followed by administration of nesiritide vs. placebo in a double blind randomized fashion. Measures of PCWP were significantly decreased and improvement in global clinical status was noted in 67% of patients on nesiritide vs. 14% on placebo. Dyspnea was reduced by 57% with nesiritide vs. 12% with placebo.[138] An evaluation of the neurohormonal response to nesiritide was also completed. The reported data confirmed a significant reduction in aldosterone and a trend toward the reduction of norepinephrine in response to nesiritide administration (Figure 24).[138] The conclusion was that nesiritide was "useful for the short-term treatment of decompensated HF."

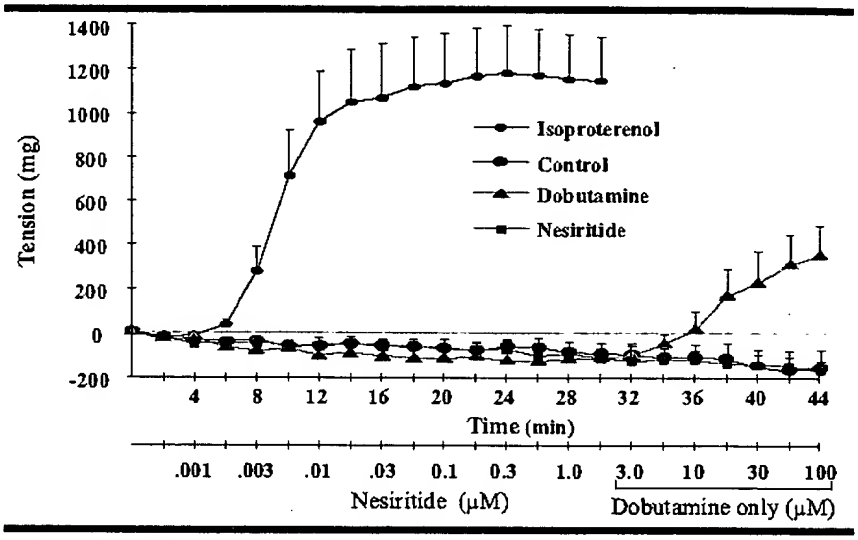

Figure 22. Comparison of inotropic effect with isoproterenol, dobutamine, and nestritide. Reprinted with permission from J *Card Fail.* 2003;9(suppl):S81.

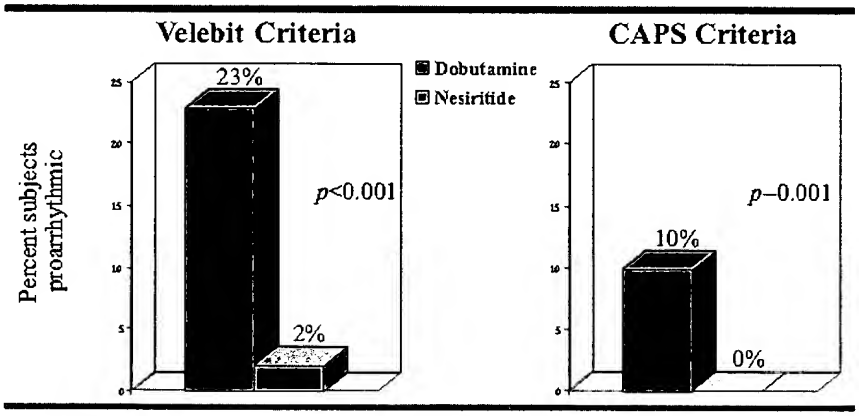

Figure 23. Comparison of proarrhythmic effects and dobutamine vs. nesiritide in heart failure patients; the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) trial. CAPS=The Cardiac Arrhythmia Pilot Study. Reprinted from J *Card Fail.* 1999;5(suppl 1).

Silver et al.[139] compared the effects of nesiritide vs. dobutamine on short-term outcomes in the treatment of patients with ADHF. Patients receiving nesiritide were on parenteral therapy for a statistically significant shorter period of time and trended to have fewer readmissions. Of note, the 6-month follow-up data demonstrated a lower mortality rate in patients originally treated with nesiritide compared with dobutamine (Figure 25). These data would suggest a benefit that extends beyond symptom relief and that includes a reduction in mortality vs. inotropes and a potential decrease in resource utilization for hospitalization.[140]

The definitive trial was the Vasodilation in the Management of Acute CHF (VMAC) trial. This was a randomized double blind trial of 489 patients admitted with ADHF. Right heart catheterization was performed in 246 patients at the investigators' discretion. Patients were randomized to nesiritide fixed dose or flexible dose (instrumented patients) vs. nitroglycerin, (dose adjusted per investigator), vs. placebo with background of standard therapy which included diuretics and may have included inotropes as well. The primary end point was the relief of dyspnea at 3 hours, which was achieved with nesiritide vs. placebo. At 24 hours,

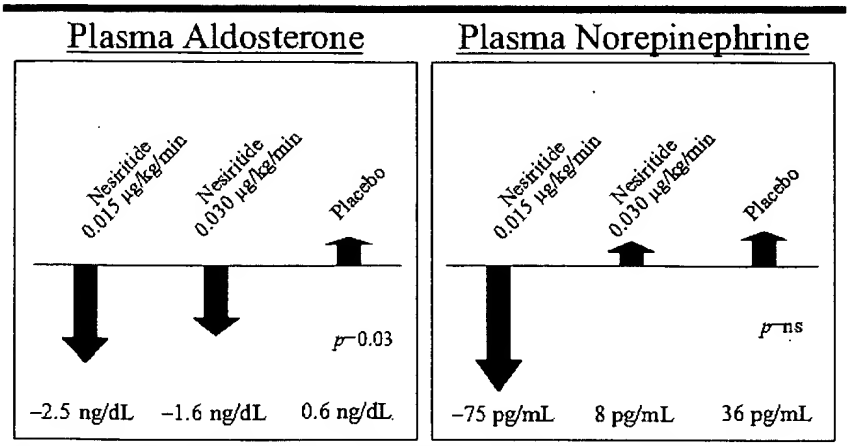

Figure 24. Effects on nesiritide on neurohormones. Figure adapted with permission from data published in *N Engl J Med.* 2000:343:246–253.[138]

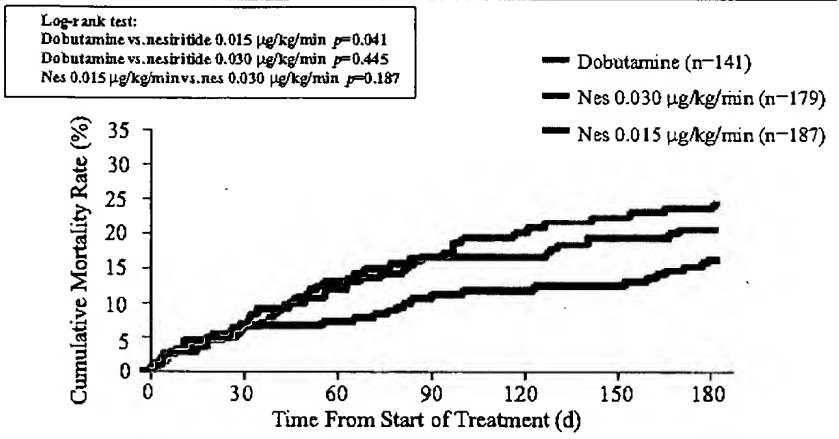

Figure 25. Effect of short-term nesiritide or dobutamine therapy on 6-month survival. Nes=nesiritide. Reprinted with permission from *J Am Coll Cardiol.* 2002;39:798–803.

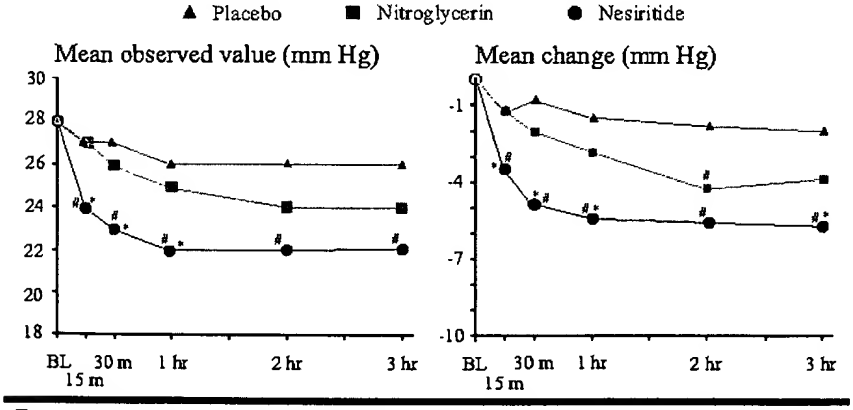

Figure 26. Vasodilation in the Management of Acute CHF (VMAC) primary end point pulmonary capillary wedge pressure through 3 hours. BL=baseline; NTG=nitroglycerin; #$p<0.05$ vs. placebo; *$p<0.05$ vs. NTG. Reprinted with permission from JAMA. 2002;287:1531–1540.[141]

the reduction in PCWP was greater for nesiritide than nitroglycerin. The conclusion was that nesiritide provided greater symptom relief and better improvement in hemodynamics than either placebo or nitroglycerin (Figure 26).[141]

Given the adverse influence of inotropes on mortality in HF, any parenteral therapy for HF must be evaluated carefully for evidence of increased mortality or other adverse risk. The totality of published data to date does not demonstrate a mortality risk of nesiritide as treatment for ADHF. Data are available from ADHERE that provide additional information on this very important topic.

Utilizing sophisticated classification and regression tree (CART) analysis statistical methodology, a comparison of outcomes within ADHERE has been completed as a function of parenteral therapies implemented. Critical to the analysis is the ability to risk adjust the data and to incorporate propensity analyses, thus accounting for adverse outcomes attributable to important comorbidities and accounting for practitioner decision making based on the absence or presence of these same comorbidities.

Within ADHERE, parenteral diuretics are utilized in 88% of all cases. Inotrope use is present in 15% of all cases and nesiritide use is now at 12% of all cases, up from 7% at the outset of ADHERE in December 2001. Risk factors for mortality in ADHERE are clustered about renal function and systolic BP. Unadjusted data that compare nesiritide to inotropes or inodilators demonstrate improved survival—a relationship that is further strengthened when the data are risk adjusted. Unadjusted data that compare nesiritide to nitroglycerin are consistent with an apparent increase in risk but once the data are adjusted for risk and propensity, there are similar outcomes seen with both nesiritide and nitroglycerin (Figure 27).[142]

The use of nesiritide is now entering the realm of advanced HF. Patients with advanced HF, NYHA class III B or IV, who are at risk for repeat hospitalization are now being evaluated as candidates for nesiritide therapy on an outpatient basis with a target of a reduction in morbidity/mortality. The recently completed Follow-up Serial Infusions of Nesiritide for HF in an Outpatient Setting (FUSION I) trial was a pilot study to test the safety of outpatient nesiritide infusions to patients

with advanced HF. Patients already demonstrated to have advanced HF and a history of recent hospitalizations were randomized to one of three arms: usual care; weekly nesiritide infusions at 0.005 µg/kg/min plus usual care; and weekly nesiritide infusions at 0.01 µg/kg/min plus usual care. In this open label randomized trial of 210 patients, nesiritide therapy was surprisingly well tolerated. Fewer than 1% of the >1600 infusions administered during the trial had to be stopped for adverse events. In a prospectively identified group of patients deemed to be at high risk based on the presence of four or more known risk factors, there was a signal of clinical efficacy with an improvement in days alive and out of hospital (Figure 28).[143] A larger 900 patient double blind randomized placebo controlled trial, FUSION II, is now underway.

Future directions for therapeutic uses of nesiritide include: post-MI to effect a decrease in LV remodeling[144]; post-cardiopulmonary bypass to mitigate postoperative renal insufficiency and to improve cardiac outcomes; pre-heart transplantation as a bridge to transplant; and a chronic ambulatory HF initiative utilizing subcutaneously administered B-type natriuretic peptide as adjunctive therapy to chronic evidence-based HF management.[145]

Therapeutic Summary. This rapidly evolving spectrum of therapeutic benefit and the emerging realm of additional therapeutic potential positions B-type natriuretic peptide as an increasingly important treatment option in the management of a growing number of cardiovascular conditions. The current approved use of nesiritide is for decompensated HF. Although guideline statements for ADHF are lacking, the totality of diagnostic and therapeutic data regarding natriuretic peptides yields an intuitively rational and reasonably evidence-based approach for the assessment and management of ADHF. A practical and clinically useful decision-making framework is suggested in Figure 29 as an adaptation of an algorithm developed by Maisel.[89]

Analysis	Nesiritide vs. NTG	Nesiritide vs. milrinone	Nesiritide vs. dobutamine
Unadjusted	**1.62***	**0.53***	**0.36***
Adjusted for covariates sex, age, BUN, SBP, DBP, CR	**0.85§**	**0.58***	**0.51***
Adjusted for covariates and propensity score	**0.83†**	**0.57***	**0.41***

Nesiritide n=2128; NTG n=3457; milrinone n=1205; dobutamine n=2211

Figure 27. Effects of IV vasoactive medications on mortality in the Acute Decompensated Heart Failure National Registry (ADHERE). NTG=nitroglycerin; BUN=blood urea nitrogen; SBP=systolic blood pressure; DBP=diastolic blood pressure; CR=creatinine; *$p \leq 0.0002$; §$p=0.24$; †$p=0.19$.

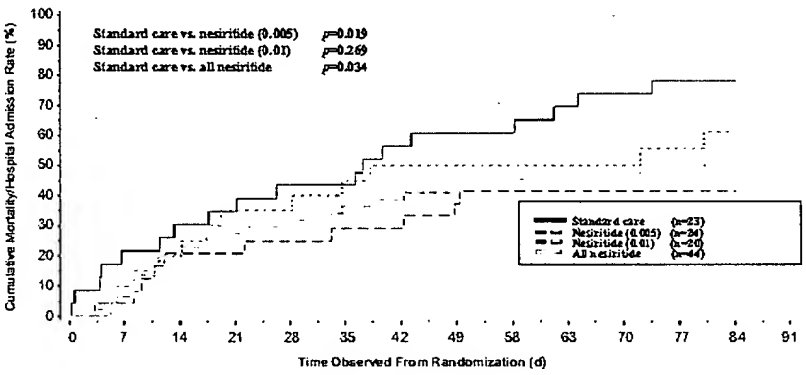

Figure 28. Relationship of mortality and hospital admission rates in treatment with nesiritide vs. standard care. Reprinted with permission from *J Am Coll Cardiol.* 2002;39:798–803.[139]

Additional Considerations

Implications of BNP Levels in the Outpatient Management of HF. Elevations of BNP have been shown to be a powerful marker for prognosis and risk stratification in the setting of HF. In a recent study[146] of 78 patients referred to an HF clinic, BNP showed a significant correlation to the HF survival score. In addition, changes in plasma BNP levels were significantly related to changes in limitations of physical activities and were a powerful predictor of functional status deterioration.

REDHOT[37] demonstrated a "disconnect" between the perceived severity of HF cases by ED physicians and severity as determined by BNP levels. Therefore, an algorithm utilizing BNP may better determine severity of congestive HF than clinical judgment alone.

ADHERE registry is the largest registry for decompensated HF, currently enrolling about 100,000 patients (Figures 30, 31). One of the most impressive findings thus far is the notion that beginning vasoactive therapy in the ED was associated with a 3.1-day reduction in hospital length of stay compared with when such therapies were not initiated until after admission. This analysis suggests that choice of therapy in the ED may critically impact the course of patients with HF.[147]

The Prospective Randomized Out comes Study of Acutely Decompensated HF Treated Initially in Outpatients with Natrecor (PROACTION) emergency medicine pilot trial of patients with acute HF randomized in the ED showed a potential benefit of using nesiritide along with standard therapy. While the

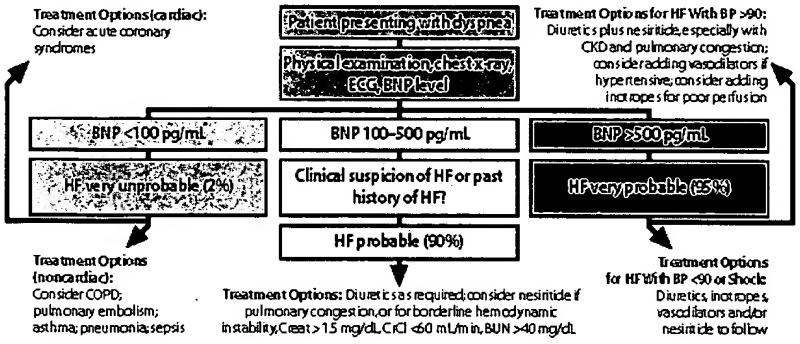

Figure 29. The evaluation and treatment of patients presenting with acute dyspnea. HF=heart failure; BP=blood pressure; ECG=electrocardiogram; BNP=B-type natriuretic peptide; COPD=chronic obstructive pulmonary disease; BUN=blood urea nitrogen; Creat=creatinine; CrCl=creatinine clearance; CKD=chronic kidney disease. ©MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. *Rev Cardiovasc Med.* 2002;3(suppl 4):S10–S17. *Reviews in Cardiovascular Medicine* is a copyrighted publication of MedReviews, LLC. All rights reserved.

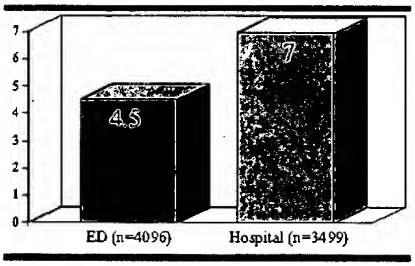

Figure 30. Relationship of hospital length of stay (days) and site of initiation of vasoactive therapies. ED=emergency department. Reprinted with permission from *Ann Emerg Med.* 2003;42(4):S26.

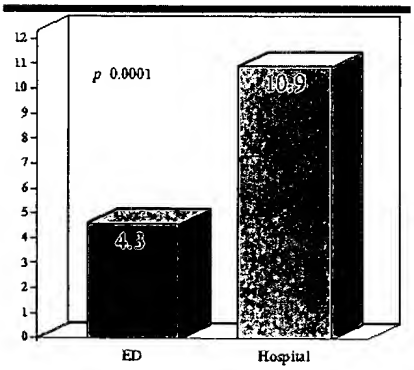

Figure 31. Relationship of in-hospital mortality and site of initiation of vasoactive therapies. ED=emergency department. Reprinted with permission from *Ann Emerg Med.* 2003;42(4):S26.

length of stay was the same for the two cohorts, in the subsequent 30 days, patients receiving nesiritide spent clinically important and statistically significantly fewer hospital days compared with standard care (2.5 vs. 6.5 days) over the next month.

Integrating BNP Levels Into a Rational Use of Nesiritide. While BNP is approved by the FDA for the diagnosis of HF, its usefulness to monitor effectiveness in treatment is still under study. However, as it appears that many hospitals and clinics are already using BNP levels to guide therapy, some suggestions can be made. One can stratify patients to the high-risk category in part using BNP levels. Fonarow's group[148] found three independent predictors of acute mortality at the index admission, derived from >80,000 patients in the ADHERE registry. They are a blood urea nitrogen >43 mg/dL, systolic BP <115 mm Hg, or a creatinine >2.75 mg/dL. Since these are each independently associated with death at the current hospitalization, the presence of any one suggests the need for aggressive therapy. Furthermore, these indicators are additive; if none are present, index visit mortality is 2.2%, compared with >22% if all three occur.

If patients are admitted with BNP levels <600 pg/mL and blood urea nitrogen levels are <40 (i.e., lower risk), one can often start with parenteral diuretics. Subsequently, the patient can be reclassified into low- or high-risk groups based on their response over the next 6–12 hours. Patients who have an adequate diuresis, a fall in BNP level, and no deterioration in renal function might opt for continued diuretics/vasodilators until euvolemia is reached. Hopefully, this will lead to a BNP <400 pg/mL. In one study, patients whose discharge BNP levels fell below 430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days.[66] If the BNP level is higher than this, the patient's volume status should be reevaluated. If it is determined that the patient is not yet euvolemic, nesiritide might be considered for 24–48 hours.

After receiving short-term parenteral diuretics, patients with an inadequate diuresis, no change, or an increase in BNP level, and worsening renal function, should be considered to be high risk. If these patients have a systolic BP of at least 90 mm Hg, they can be given 24–48 hours of nesiritide therapy along with IV diuretics. BNP levels can then be checked several hours after cessation of nesiritide. IV or oral diuretics and vasodilators can then be used until euvolemia is achieved.

Patients with systolic BPs <90 mm Hg often need vasopressors and/or inotropes, sometimes under Swan-Ganz catheter monitoring guidance. In our experience, if these patients show improvement in BP and symptoms, they can then be transitioned to nesiritide. If there is no improvement on inotropes or pressors, further invasive strategies need to be considered. Finally, it is conceivable that in patients who are admitted with very high BNP levels and impaired renal function, nesiritide could be started immediately.

Toward the Future: Monitoring BNP Levels Post-Hospitalization—Implications for BNP-Guided Outpatient Treatment. Perhaps an important marker for rehospitalization risk is a post-discharge rise in BNP. Early after discharge, rise in BNP levels often are associated with volume overload and diuretics may need to be adjusted. As is the practice at several institutions,[149] when a patient with HF comes to the urgent care center with symptoms that could represent a decompensated state,

a BNP level is drawn. If no different from baseline values, then decompensation is unlikely. How high a BNP should be over baseline to call it decompensated is not known. As BNP should not be used without clinical context, it should be used in conjunction with other features of the history and physical exam (clinical features of decompensation along with an increase of 50% or more from baseline are often associated with decompensation in the panel's experience).

The correlation between the drop in BNP level and the patient's improvement in symptoms (and subsequent outcome) during hospitalization suggests that BNP-guided treatment might make "tailored therapy" more effective in an outpatient setting such as a primary care or cardiology clinic. The Australia-New Zealand HF Group[150] analyzed plasma neurohormones for prediction of adverse outcomes and response to treatment in 415 patients with LV dysfunction randomly assigned to receive carvedilol or placebo. They found that BNP was the best prognostic predictor of success or failure of carvedilol use. Recently, Troughton et al.[151] randomized 69 patients to NT-BNP–guided treatment vs. symptom-guided therapy. Patients receiving NT-BNP–guided therapy had lower NT-BNP levels along with reduced incidence of cardiovascular death, readmission, and new episodes of decompensated HF. This study has spawned a number of larger studies including the multicenter Rapid Assessment of Bedside BNP In Treatment of HF (RABBIT) trial. It is evident that patients with poor ejection fraction but with BNP levels that are <200 pg/mL have a very good prognosis. A study of 452 ambulatory patients with an LV ejection fraction <35% found that in patients with mild-to-moderate HF (NYHA functional class I/II), BNP levels were independent predictors of sudden death, an important cause of mortality in these patients. They found that a cutoff BNP level of 130 pg/mL differentiated between patients with high and low survival rates of sudden death. Only 1% (1 of 110) of those patients with BNP levels below the cutoff point died suddenly, in comparison to a sudden death rate of 19% (43 of 227) among those patients with BNP levels above the cutoff point.[74] Using BNP levels to identify a patient population with a higher risk of sudden death can help to tailor their treatment and extend survival.

It also appears that angiotensin converting enzyme inhibitors, angiotensin-receptor blocker agents, aldosterone antagonists, and perhaps β blockers drive BNP levels down, although it is unclear whether this is a true marker of clinical improvement. In Val-HeFT, changes in BNP over time induced by pharmacologic therapy were shown for the first time to correlate with morbidity and mortality.[152] Patients with the greatest percentage decrease in BNP and norepinephrine from baseline had the lowest morbidity and mortality, whereas patients with the greatest percentage increase in BNP and norepinephrine were at the greatest risk. The authors found BNP to be more predictive of morbidity and mortality than norepinephrine or, in a separate analysis, than aldosterone.[153]

The current practice of some physicians is to aim for BNP levels <200–300 pg/mL with standard therapy of angiotensin-converting enzyme inhibitors and β blockers and diuretics. Patients with BNP levels between 200 and 500 pg/mL are often NYHA functional class II/III and may require more diuretics, especially spironolactone. Patients who, despite standard medical treatment, have advanced symptoms along with high BNP levels (400–600 pg/mL) might be candidates for continuous and palliative outpatient infusions of inotropes or nesiritide, biventricular pacing (if QRS >120–130 ms), cardiac transplantation, or LV assist device. In the future stem cell or gene therapy may have a role in treatment of these patients.

Toward Earlier Attention to Rising BNP Levels—Evaluations of Outpatient Nesiritide Infusions. The Follow Up Serial Infusions of Natrecor (FUSION) trial[143] was a multicenter, randomized, open-label study in which 210 HF patients at high risk of hospitalization were randomized to one of three treatment arms: standard care (consisting of long-term cardiac medications with or without IV inotropes) or serial infusions of either 0.005 or 0.01 μg/kg/min nesiritide in addition to their usual long-term cardiac medications, excluding IV inotropes. The study demonstrated that weekly infusions of nesiritide in the outpatient setting were well tolerated and associated with few deaths and hospitalizations as well as improvement in NYHA functional class and overall clinical status. If the benefits seen in FUSION on clinical outcomes such as mortality and hospitalizations are replicated in a larger trial, nesiritide has the potential to become an effective outpatient treatment for hundreds of thousands of patients with advanced chronic HF. The likely trigger for outpatient infusions would include symptoms of decompensation along with a rising BNP level.

Conclusions

The data presented and reviewed above are likely to represent a small percentage of our knowledge about the natriuretic peptide system as it unfolds in the months and years ahead. Nonetheless, it is clear that this important homeostatic system impacts so specifically the cardiovascular system that all interested in heart and blood vessel disease must remain cognizant of the advances in this discipline. The Panel hopes we have contributed to the current understanding of this area.

We hope that after reading this document you have a heightened interest and understanding of the importance and ramifications of the natriuretic peptide system. We will continue to follow the developments in this area and update this consensus as new research becomes available.

The Consensus Statements are available in pocket accordion format. For copies please contact your local representative from:

Abbott Laboratories Diagnostics Division, Bayer HealthCare Diagnostics Division, Biosite, or SCIOS.

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CHF, Inc.
Three Parklands Drive, Darien, CT 06820 USA
Tel (203) 656-1711 • Fax (203) 656-1717
www.lejacq.com

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Briefs and Other Related Documents

United States Court of Appeals,
Federal Circuit.
STRATOFLEX, INC., Appellee,
v.
AEROQUIP CORPORATION, Appellant.
Appeal No. 83-587.

July 25, 1983.

Action was brought for judgment declaring invalid and noninfringed a patent for tubing used in the aircraft and missile industry to convey pressurized fuel, lubricants, and other fluids. The United States District Court for the Eastern District of Michigan, 561 F.Supp. 618, Patricia J. Boyle, J., declared certain claims of the patent invalid and not infringed, and appeal was taken. The Court of Appeals for the Federal Circuit, Markey, Chief Judge, held that the evidence was sufficient to sustain the finding that claims Nos. 1, 3, 4, 6 and 7 of patent No. 3,473,087 for the tubing were invalid for obviousness.

Affirmed.

West Headnotes

[1] **Patents ⇐312(1.2)**
291k312(1.2) Most Cited Cases
(Formerly 291k312(1.8), 291k312(1), 291k312, 291k312(.8))
Party asserting invalidity of a patent not only has procedural burden of proceeding first and establishing a prima facie case, but burden of persuasion on the merits remains with that party until final decision; party supporting validity has no initial burden to prove validity, having been given procedural advantage requiring that he come forward only after a prima facie case of
invalidity has been made. 35 U.S.C.A. § 282.

[2] **Patents ⇐33**
291k33 Most Cited Cases
Evidence rising out of "secondary considerations" must always when present be considered en route to a determination of obviousness of a patent, and it is error to exclude that evidence from consideration. 35 U.S.C.A. § 103.

[3] **Patents ⇐36(1)**
291k36(1) Most Cited Cases
Nexus is required between merits of a claimed invention and the evidence offered if that evidence is to be given substantial weight en route to conclusion on the obviousness issue. 35 U.S.C.A. § 103.

[4] **Patents ⇐312(5)**
291k312(5) Most Cited Cases
Evidence sustained finding that claims Nos. 1, 3, 4, 6, and 7 of patent No. 3,473,087 for tubing used in the aircraft and missile industry to convey pressurized fuel, lubricants, and other fluids were invalid for obviousness. 35 U.S.C.A. § 103.

Patents ⇐328(2)
291k328(2) Most Cited Cases
2,108,759, 2,341,360, 2,632,205, 2,645,249, 2,685,707, 2,752,637, 2,781,288, 2,863,174, 2,945,265, 3,070,132. Cited as prior art.

Patents ⇐328(2)
291k328(2) Most Cited Cases
3,166,688, 3,658,976. Cited.

Patents ⇐328(2)
291k328(2) Most Cited Cases
3,473,087. Claims 1, 3, 4, 6, and 7 invalid and not infringed.
***1531** Don K. Harness, and Richard A. Walker, Birmingham, Mich., of counsel for appellant. With them on the brief was Jerry K. Harness, Jackson, Mich.

William A. Marshall, Chicago, Ill., argued for appellee. With him on the brief was Donald J. Brott, Chicago, Ill.

Before MARKEY, Chief Judge, and DAVIS and BALDWIN, Circuit Judges.

MARKEY, Chief Judge.

Appeal from a judgment of the District Court for the Eastern District of Michigan, 561 F.Supp. 618, declaring Claims 1, 3, 4, 6, and 7 of U.S. Patent No. 3,473,087 to Winton Slade ('087 patent) invalid and not infringed. We affirm.

When Stratoflex filed suit seeking a declaration of invalidity and non-infringement of the '087 patent, Aeroquip, as assignee, counterclaimed for infringement of claims 1, 3, 4, 6, and 7. After a non-jury trial, Judge Boyle declared those claims invalid and found them not infringed. [FN1]

> FN1. Though Stratoflex filed for a declaratory judgment that the *patent* was invalid, trial, judgment, and the briefs on appeal dealt only with claims 1, 3, 4, 6, and 7. Accordingly, we make no holding respecting validity of claims 2, 5, and 8-19.

II. *Background*

A. *The Technology*

Stratoflex and Aeroquip manufacture electrically conductive polytetrafluoroethylene (PTFE) [FN2] tubing used in the aircraft and missile industry to convey pressurized fuel, lubricants, and other fluids.

> FN2. The parties refer to polytetrafluoroethylene also as "Teflon," a registered trademark of the E.I. Dupont de Nemours Company.

PTFE has replaced organic and synthetic rubbers and plastic in fuel hoses because it has a number of superior characteristics. ***1532** Though pure PTFE is dielectric (non-conductive), it can be made with fillers to make it conductive, though the "filled" tubing is more susceptible to leakage when voids form between the PTFE and filler particles.

B. *The Invention*

The Slade invention relates to a composite PTFE tubing, formed of an inner layer of electrically conductive PTFE having particles such as carbon black uniformly distributed in it and an outer layer of essentially pure non-conductive PTFE. Claims 1 and 7 are representative:

1. A tubular extrudate formed of attached concentric tubular extrusions, the inner tubular extrusion comprising associated particles of unsintered tetrafluoroethylene polymer and pulverulent, inert, electrically conductive particles, and the outer tubular extrusion comprising associated particles of unsintered tetrafluoroethylene polymer.

7. A tube of polytetrafluoroethylene and the like for conducting fluids under pressure and including means for discharge of internal static electricity to the ends of the tube and grounding the same from the tube interior at said ends in order to maintain the polytetrafluoroethylene tubing performance characteristics, said tubing having an integral polytetrafluoroethylene wall structure with an interior liner portion of a substantially annular conformation from end to end and having a uniform dispersion of electrically conductive particles embedded therein, the major portion of said tubing wall completely surrounding said liner portion exteriorly and being relatively nonconductive in character, said surrounding portion together with said liner containing fluid under pressures uniformly within said tubing.

Claims 3, 4, and 6 are similar to claim 1, but specify various percentages of ingredients.

The particles in the inner layer of the claimed tubing dissipate electrostatic charges built up on the inner surface of the tubing, conducting them lengthwise of the tubing to grounded metal fittings at the ends of a hose assembly of which the tubing is part, to prevent arcing or discharging through the tubing wall to the surrounding metal braid. Arcing causes "pin holes" through which fuel can leak. The outer layer is coextruded or bonded around the inner layer to contain any fuel leaking through the inner layer. The composite tubing has excellent conductivity, while retaining the desirable characteristics of PTFE tubing.

C. *Events Leading to the '087 Patent*

Pure PTFE tubing had been used successfully in aircraft engines since at least 1956. In 1959, with the introduction of hydrocarbon jet fuels, leaks were noticed. Aeroquip assigned two staff engineers, Abbey and Upham, to determine the cause. They found the problem to be the arcing of electrostatic charges through the wall of the pure dielectric PTFE tubing to create "pin holes" as described above.

Abbey and Upham found the "pin hole" phenomenon exhibited by all three types of PTFE (White-Titeflex; Pink/Red-Aeroquip; Black-Goodrich) used in aircraft engines. The black tubing appeared superior because the carbon black it contained gave it an intermittent conductivity. The carbon black took the form of discontinuous strings and arcing across the spaces between string ends conveyed charges to the ends of the tubing. Electrical erosion of the strings, however, widened the spaces, destroying conductivity and leading to the "pin hole" phenomenon. Abbey and Upham concluded that susceptibility of PTFE tubing to "pin holing" was proportional to its conductivity, and that carbon black increased the conductivity of PTFE tubing.

In early 1960, having determined the cause of leaking, Aeroquip approached Raybestos-Manhattan (Raybestos), a PTFE hose manufacturer, for a solution. Aeroquip later purchased the hose section of Raybestos, obtaining the Slade patent by mesne assignment.

***1533** Raybestos assigned the project to the inventor, Winton Slade, who prepared several samples of conductive PTFE tubing (powdered lead, copper, chemically etched, and carbon black) and sent them for testing to Aeroquip in the summer of 1960. In the Fall, Aeroquip ordered a small production quantity of carbon black tubing. That tubing was not a composite and the carbon black was not uniformly distributed in it.

Slade conceived of the composite tube of the invention as early as August 5, 1960 and reduced it to practice in November of 1961. He filed a patent application on May 22, 1962, with claims directed to the composite tubing and also to various processes for making it.

During prosecution, Slade's assignee Raybestos sought and was denied declaration of an interference with a patent application assigned to Titeflex. The Titeflex application issued as U.S. Patent 3,166,688 ('688 patent). Raybestos then was granted an interference with claims 1 and 2 of the '688 patent. An agreement provided that the loser of the interference would receive a royalty free license. Slade was awarded priority and Titeflex was licensed.

When the examiner imposed a restriction requirement on the Slade application, Slade elected to prosecute the product claims, and filed the process claims in a co-pending application which issued as U.S. Patent No. 3,658,976. Slade's original application issued with its product claims as the '087 patent on October 1, 1969.

D. *Stratoflex Actions*

From 1962 to 1970, Stratoflex purchased PTFE tubing containing carbon black from B.F. Goodrich. When Goodrich ceased production, Stratoflex purchased conductive PTFE tubing made by Titeflex under its license. Stratoflex then began manufacturing and selling its own "124" and "127" composite tubing having an inner layer with conductive carbon black uniformly dispersed throughout, and an outer layer that is essentially nonconductive, though that outer layer includes a small amount of carbon black to color the tubing and to aid extrusion.

On December 8, 1978, Aeroquip charged that Stratoflex's unauthorized manufacture and sale of "124" and "127" tubing infringed its rights under the '087 patent.

E. *Trial and Opinion*

Trial was held on December 15, 16, 18, 19 and 22, 1980. Stratoflex alleged that the '087 patent was invalid as anticipated under 35 U.S.C. § 102, as having been in public use or on sale, 35 U.S.C. § 102(b); for obviousness, 35 U.S.C. § 103; or because the claims were indefinite, 35 U.S.C. § 112. Judge Boyle decided the validity issue on 35 U.S.C. § 103, and the appeal concerns only that Section.

On August 16, 1982, Judge Boyle issued judgment and an accompanying opinion. In that opinion, Judge Boyle indicated: that the presumption of validity is weakened when the challenger introduces pertinent prior art not considered by the examiner; that Aeroquip was therefore not entitled to the presumption's full benefit; that the relevant prior art included rubber hose; that one of ordinary skill in the art had a degree in chemical engineering or its equivalent and substantial experience in the extrusion art; that the prior art

taught addition of conductive carbon black to tubing to dissipate electrostatic charges on its inner surface; that composite tubing incorporating various materials in each layer to yield superior products was known; that addition of carbon black to PTFE to induce conductivity was known; that the only differences between the claims and the prior art were use of PTFE in concentric tubes and the "salt and pepper" method of forming the inner tube layer; that secondary considerations were not to be considered because the claimed inventions were clearly obvious and "those matters without invention will not make patentability;" that those matters should be considered only in a close case where they could "tip the balance in favor of patentability;" that it was unnecessary ***1534** to determine whether synergism was a separate requirement for validity "since either standard justifies a conclusion that the combination of these elements simply lacks 'the unique essence of authentic contribution' to the (PTFE) art which is the heart of invention;" that Stratoflex did not infringe claims 1, 3, 4, 6 or 7 because the only non-obvious difference between the claims and the prior art was the "salt and pepper" process for making the tubing layer and Stratoflex did not use that process.

Issues

Whether Judge Boyle erred in: (1) declaring claims 1, 3, 4, 6, and 7 invalid; (2) finding non-infringement.

I. VALIDITY

(A) *Presumption of Validity*

The law, 35 U.S.C. § 282, provides:

> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though defendant upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

[1] *See, also, Solder Removal Co. v. USITC*, 582 F.2d 628, 65 CCPA 120, 199 USPQ 129, 133 (CCPA, 1978). The presumption, like all legal presumptions, is a procedural device, not substantive law. It does require the decisionmaker to employ a decisional approach that starts with acceptance of the patent claims as valid and that looks to the challenger for proof of the contrary. Thus the party asserting invalidity not only has the procedural burden of proceeding first and establishing a prima-facie case, but the burden of persuasion on the merits remains with that party until final decision. The party supporting validity has no initial burden to prove validity, having been given a procedural advantage requiring that he come forward only after a prima-facie case of invalidity has been made. With all the evidence in, the trial court must determine whether the party on which the statute imposes the burden of persuasion has carried that burden. [FN3]

> FN3. If that burden is not carried, the trial court need only so state. It is not necessary to hold "valid" a patent that on another record may be shown to have been invalid. If the burden imposed by § 282 is carried, the patent should be declared invalid.

Introduction of more pertinent prior art than that considered by the examiner does not, therefore, "weaken" or "destroy" the presumption. Nor does such introduction "shift" the basic burden of persuasion. The presumption continues its procedural, burden-assigning role throughout the trial. Such introduction can, of course, facilitate the validity challenger's carrying of that burden. It would require one supporting validity to come forward with countervailing evidence, as would the introduction of any evidence tending to establish invalidity. In the end, the question is whether *all* the evidence establishes that the validity challenger so carried his burden as to have persuaded the decisionmaker that the patent can no longer be accepted as valid.

The error here, in denying Aeroquip the "benefit" of the presumption, was more rhetorical than substantive, and did not in this case rise to a level requiring reversal. The record does not indicate that Judge Boyle placed a burden of proving validity on Aeroquip. On the contrary, her full and exhaustive consideration of the prior art indicated a careful evaluation of the case made by the burden-bearing Stratoflex. We have, of course, reviewed the record here in light of the burden assigned Stratoflex by 35

U.S.C. § 282. [FN4]

FN4. On the infringement issue, the burden is borne throughout by the patent owner (or exclusive licensee).

***1535** (B) *Obviousness*

The declaration that claims 1, 3, 4, 6, and 7 of the '087 patent are invalid was based on a conclusion that the inventions set forth in those claims would have been obvious under 35 U.S.C. § 103, in the light of facts found in the course of following the guidelines set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693, 15 L.Ed.2d 545 (1966).

Aeroquip contends that error occurred in findings on the scope and content of the prior art, level of ordinary skill, and differences between the prior art and the claimed invention, and in the legal conclusion of obviousness based on those findings.

Judge Boyle said, "[T]he question of obviousness is a mixed question of fact and law requiring factual findings," citing the then-applicable view expressed by the Court of Appeals for the Sixth Circuit. In this court, the obviousness determination is "a legal conclusion based on factual evidence." *Stevenson v. International Trade Commission*, 612 F.2d 546, 67 CCPA 109, 204 USPQ 276 (CCPA 1979). The difference does not affect the outcome on this appeal, because it did not in this case lead to error in either the findings or conclusion.

Under Rule 52(a), Federal Rules of Civil Procedure, our review of the findings undergirding the conclusion on obviousness is limited to a determination of whether they were clearly erroneous in light of the entire record.

Scope and Content of the Prior Art

Aeroquip contends that the scope of the relevant prior art excludes rubber hose because PTFE is a unique material, possessing properties that differ significantly from rubber, and that, because the claims are limited to PTFE, the rubber hose art could at most be peripherally relevant as background information.

The scope of the prior art has been defined as that "reasonably pertinent to the particular problem with which the inventor was involved." *In re Wood*, 599 F.2d 1032, 1036, 202 USPQ 171, 174 (Cust. & Pat.App.1979), *see Weather Engineering Corp. of America v. United States*, 614 F.2d 281, 222 Ct.Cl. 322, 204 USPQ 41 (Ct.Cl.1980). The problem confronting Slade was preventing electrostatic buildup in PTFE tubing caused by hydrocarbon fuel flow while precluding leakage of fuel. None of the unique properties of PTFE would change the nature of that problem. Nor would anything of record indicate that one skilled in the art would not include the rubber hose art in his search for a solution to that problem.

Indeed, Slade himself referred to a standard textbook on conductive carbon black in rubber when he began his search for a solution. Judge Boyle correctly found Slade's act an acknowledgement by the problem solver of what he considered relevant prior art.

The examiner cited two prior art references in the rubber hose art, one disclosing the problem of electrostatic buildup caused by fuel flow. The Abbey-Upham report, though concerned with PTFE, included a conductivity comparison with carbon black filled rubber hose, and its bibliography listed several articles on electrostatic buildup in rubber. The record reflects that PTFE and rubber are used by the same hose manufacturers to make hoses and that the same and similar problems have been experienced with both. There is no basis for finding that a solution found for a problem experienced with one material would not be looked to when facing a problem with the other. The finding that the rubber hose art is relevant and thus within the scope of the art was not clearly erroneous.

The content of the prior art included the Abbey-Upham Report and several patents relating to conductive and composite rubber hose and to PTFE tubing.

The Abbey-Upham Report, as above indicated, discloses the cause of PTFE tubing "pin holes" as the arcing of electrostatic charges laterally through the non-conductive PTFE tubing wall to the surrounding metal braid, that carbon black increases conductivity of PTFE, and that susceptibility of PTFE tubing to "pinholing" is directly proportional to its conductivity. Judge ***1536** Boyle correctly found the report to

have disclosed the basic concepts underlying the claimed invention, but not that of forming PTFE tubing as a composite having a conductive inner layer and a nonconductive outer layer.

United States Patent No. 2,341,360 ('360 patent) teaches composite tubing having carbon black in one layer to make it electrically conductive for dissipation of static electricity.

U.S. Patent No. 2,632,205 ('205 patent) teaches a rubber or plastic composite tubing for conveying fluids and having powdered metal or other conductive materials embedded along the inner wall to conduct electric charges lengthwise of the tubing.

U.S. Patent No. 3,070,132 teaches extrusion of carbon black mixed with plastic to form a continuous conductive stripe in a normally dielectric tubing to prevent accumulation of electrostatic charges. It teaches that electrostatic discharge causes leaks through the wall of the tubing and explosions when inflammable materials are conveyed. It mentions rubber tubing.

U.S. Patent No. 2,108,759 discloses an "antistatic" fuel nozzle. It teaches dissipation of electrostatic charges caused by hydrocarbon fuel flow, before those charges can arc, by employing conductive materials like synthetic rubber in an inner layer of the nozzle.

U.S. Patent No. 2,781,288 ('288 patent) teaches a composite rubber hose with each layer arranged to take advantage of its particular properties. It suggests carbon black as a filler, but not as a conductor.

U.S. Patent No. 2,645,249 ('249 patent) and U.S. Patent No. 2,501,690 ('690 patent) teach composite tubing with each layer containing different fillers to impart varying characteristics to the inner and outer layers.

U.S. Patent No. 2,863,174, U.S. Patent No. 2,685,707, and U.S. Patent No. 2,752,637 disclose the use of carbon black as an extrusion aid in forming PTFE.

U.S. Patent No. 2,945,265 ('265 patent) teaches coextrusion of PTFE with different fillers, carbon black being used as a coloring agent.

Aeroquip's attack on the content-of-the-prior-art findings is limited to its argument that rubber hose should be excluded. That argument having been found wanting, the findings on the content of the prior art cannot be viewed as clearly erroneous.

Consideration of the scope and content of the prior art tilts the scales of decision toward a conclusion of obviousness. Thus the Abbey-Upham report teaches use of carbon black to increase conductivity of PTFE tubing to reduce the chance of electrostatic buildup on the tubing wall. It would appear to have been obvious to one skilled in the art to place the conductive material in the wall where the electrostatic buildup occurs (here the inner wall subjected to electrostatic buildup by fuel flow) as suggested by the '360 and '205 patents. It would appear to have been obvious from the '288, '249, and '690 patents to form a composite tubing with layers arranged to take advantage of their physical and chemical properties. On this record, consideration of the prior art as a whole, and in the absence of evidence that any special problem in following its teachings was created by the unique properties of PTFE, it would appear to have been obvious to place a conductive PTFE layer inside an essentially non-conductive outer PTFE layer to prevent fuel seepage associated with the conductive layer.

Differences Between the Claimed Invention and the Prior Art

Though claim 7 differs substantially from the others, claims 1, 3, 4, 6, and 7 have not been argued separately. They therefore stand or fall together. *In re Bayer*, 568 F.2d 1357, 196 USPQ 670 (Cust. & Pat.App.1978).

Aeroquip concedes that pure PTFE had been known to be dielectric, that carbon black was known to be conductive, and that PTFE had been made into tubing containing at least a small amount of carbon black. It alleges that the prior art does not show the composite tubing set forth in the claims, ***1537** specifically a composite PTFE tubing with its inner layer formed of uniformly distributed carbon black and PTFE, to provide conductivity sufficient to dissipate electro-

static buildup, and an outer layer of relatively pure PTFE that prevents fuel leakage. It is true that no single reference shows all elements of the claims, but the holding here is one of invalidity for obviousness, not for anticipation. The question, therefore, is whether the inventions set forth in claims 1, 3, 4, 6 and 7, each as a whole, would have been obvious to one of ordinary skill in the art when they were made, in view of the teachings of the prior art as a whole.

Though findings on the "differences" from the prior art are suggested by *Graham v. John Deere*, supra, the question under 35 U.S.C. § 103 is not whether the differences *themselves* would have been obvious. Consideration of differences, like each of the findings set forth in *Graham*, is but an aid in reaching the ultimate determination of whether the claimed invention *as a whole* would have been obvious.

Judge Boyle found that the differences between the claimed invention and the prior art were use of *PTFE* in concentric tubes and the "salt and pepper" process of forming the inner layer. The first difference would indicate a mere change of material. The second difference is, of course, irrelevant as stated, the claimed inventions having nothing to do with the process of making the inner layer. The finding may have been meant to indicate that the second difference lay in the structural *result* of the "salt and pepper" process, namely a uniform dispersion of carbon black particles in the inner layer (a limitation appearing only in claim 7).

With respect to use of a different material, the problem (leakage) and the cause ("pin holes" from electrostatic charges) were known with respect to that material (PTFE). A solution for the electrostatic charge problems, i.e., dissipation of charges lengthwise of the tubing, was known. Nothing in the first difference found would indicate that it would have been nonobvious to transfer that solution from tubing formed of other materials to tubing formed of PTFE. As above indicated, no special problem needed to be or was overcome in substituting a different material (PTFE) for the materials (rubber and plastics) of the prior art.

Similarly, with respect to uniform dispersion of conductive particles, it was known that spaces between carbon black areas in tubing permit arcing. Nothing of record establishes that use of uniform dispersion to limit or eliminate such spaces would not have been obvious. The same is true respecting use of a nonconductive outer layer to contain leakage from the inner conductive layer.

Aeroquip challenges the finding that the Abbey-Upham report does not teach away from use of carbon black in PTFE tubing, citing this language in the report: "The possibility of establishing continuous longitudinal strings of carbon particles during extrusion, especially in view of the relatively small percentage of carbon black used in Teflon hose seemed remote." It appears between two others in a segment having a thrust quite opposite from that suggested by Aeroquip:

> "An explanation of this intermittent conductive behavior required some further investigation. The possibility of establishing continuous longitudinal strings of carbon particles during extrusion, especially in view of the relatively small percentage of carbon black used in Teflon hose seemed remote. If, however, the carbon particle strings were discontinuous, and the individual particles were distributed at varying distances from each other, the intermittent conduction observed in the carbon black filled tubes could be easily understood."

Investigators Abbey and Upham were speculating on the cause of intermittent conductivity in a PTFE tube containing carbon black. They rejected as "remote" the ***1538** possibility that in *extruding* the tubing the carbon formed continuous strings because there was a small percentage of carbon present. That sentence dealt with a process of making the tubing. As subsequently proven in the report, a better explanation was the presence of discontinuous strings in the tubing under investigation.

In the sentence following that cited to us by Aeroquip, the Abbey-Upham report describes uneven spacing between carbon black particles as a possible cause of intermittent conductivity. Far from "teaching away," therefore, the report may be viewed as pointing in the direction of uniform dispersion of such particles, as set forth in claim 7, to produce less

intermittent conductivity. [FN5]

> FN5. Aeroquip's argument that simplicity will not establish obviousness is true but irrelevant. Judge Boyle did not base her obviousness conclusion on simplicity.

The findings that the differences here were use of a different material and uniform dispersion of carbon black particles were not clearly erroneous. Those differences do not tilt the scales toward a conclusion of nonobviousness of the invention as a whole in light of all prior art teachings summarized above.

Level of Ordinary Skill

The district court found the level of ordinary skill to be that of a chemical engineer or equivalent, having substantial experience in the extrusion arts. Aeroquip says that was too high, suggesting that of an engineer or technician in the PTFE art, as described by its expert, Townsend Beaman. The suggestion is but another effort to limit the prior art to PTFE tubing and avoid inclusion of the art of making fuel hoses of other materials.

The level of ordinary skill may be determined from several factors. *Orthopedic Equipment Company v. United States*, 702 F.2d 1005, 217 USPQ 193 (Fed.Cir.1983) *see Jacobson Brothers Inc. v. United States*, 512 F.2d 1065, 206 Ct.Cl. 518 (Ct.Cl.1975). Slade had the level of skill set by the district court. Stratoflex witness Linger was a mechanical engineer with years of experience in the rubber and PTFE hose art. Mr. Beaman was patent counsel for Aeroquip. Judge Boyle correctly viewed Beaman as an observer of, not a worker in, the relevant art.

The statute, 35 U.S.C. § 103, requires that a claim be declared invalid only when the invention set forth in that claim can be said to have been obvious "to one of *ordinary* skill in the art." (emphasis added) As an aid in determining obviousness, that requirement precludes consideration of whether the invention would have been obvious (as a whole and just before it was made) to the rare genius in the art, or to a judge or other layman after learning all about the invention.

Aeroquip has not shown the finding on the level of ordinary skill in the art to have been erroneous here.

Secondary Considerations

[2] It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included. Thus evidence rising out of the so-called "secondary considerations" must always when present be considered en route to a determination of obviousness. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed.Cir.1983) citing *In re Fielder and Underwood*, 471 F.2d 640, 176 USPQ 300 (Cust. & Pat.App.1973), *see In re Mageli et al.*, 470 F.2d 1380, 1384, 176 USPQ 305, 307 (Cust. & Pat.App.1973) (evidence bearing on issue of nonobviousness "is never of 'no moment', is always to be considered and accorded whatever weight it may have.") Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, ***1539** not just when the decision-maker remains in doubt after reviewing the art.

Judge Boyle made findings on secondary considerations, but said she did not include them in her analysis because she believed the claimed inventions were plainly obvious and "those matters without invention will not make patentability" and should be considered only in a close case. That was error.

Enroute to a conclusion on obviousness, a court must not stop until *all* pieces of evidence on that issue have been fully considered and each has been given its appropriate weight. Along the way, some pieces will weigh more heavily than others, but decision should be held in abeyance, and doubt maintained, until all the evidence has had its say. The relevant evidence on the obviousness-nonobviousness issue, as the Court said in *Graham*, supra, and as other courts had earlier emphasized, includes evidence on what has now been called "secondary considerations." It is error to exclude that evidence from consideration.

The error may have arisen from the circuity of the slogan oft-cited as a basis for exclusion. In the slogan as here stated: "those matters" is a synonym for "evidence of nonobviousness;" the issue is "nonobviousness" not "invention;" [FN6] and "patentability"

here is a synonym for "nonobviousness." Thus the slogan reads "evidence of nonobviousness without nonobviousness will not make nonobviousness."

> FN6. See Rich, J., *Laying the Ghost of the "Invention" Requirement,* APLA Quarterly Journal, Vol. 1, No. 1, 1972, pp. 26-45.

The evidence and findings on secondary considerations being present in the record, the interests of judicial economy dictate its consideration and evaluation on this appeal. The result being unchanged, a remand for reconsideration of the evidence would in this case constitute a waste of resources for the courts and the parties.

[3] A nexus is required between the merits of the claimed invention and the evidence offered, if that evidence is to be given substantial weight enroute to conclusion on the obviousness issue. *Solder Removal Co. v. USITC,* 582 F.2d 628, 637, 65 CCPA 120, 199 USPQ 129, 137 (CCPA 1978) and cases cited therein.

Aeroquip says commercial success is shown because: the "entire industry" makes the tubing claimed in the '087 patent; only Stratoflex is not licensed under the '087 patent; Curtiss-Wright retrofitted 10,000 engines with conductive tubing; and military specifications for conductive tubing are met only by tubing claimed in the '087 patent. We are not persuaded.

Recognition and acceptance of the patent by competitors who take licenses under it to avail themselves of the merits of the invention is evidence of nonobviousness. Here, however, Aeroquip does not delineate the make-up of the "entire industry." The record reflects only two manufacturers, Titeflex and Resistoflex, in addition to the parties. Titeflex has a royalty-free license, resulting from the interference settling agreement described above. Resistoflex has a license that includes several other patents and the right to use the trademark "HI-PAC" for complete hose assemblies. Aeroquip has shown neither a nexus between the merits of the invention and the licenses of record, nor that those licenses arose out of recognition and acceptance of the patent.

No evidence of record establishes that tubing covered by the claims of the '087 patent was used in the Curtiss-Wright retrofit. It cannot therefore be given weight in respect of commercial success.

The military specifications were promulgated after the claimed invention was known. Thus the invention did not meet a longfelt but unfilled need expressed in the specifications. Moreover, the record does not support Aeroquip's assertion that the specifications can be met only by tubing covered by the claims of the '087 patent. The nexus required to establish commercial success is therefore not present with respect to the military specifications.

***1540** Nor is there evidence that others skilled in the art tried and failed to find a solution for the problem. Aeroquip cites Abbey and Upham, but their effort was limited to investigation of the problem and its cause, and was not directed to its solution.

Upon full consideration of the evidence respecting the secondary considerations in this case, and of Aeroquip's arguments, we are persuaded that nonobviousness is not established by that evidence. Judge Boyle's error in refusing to include that evidence in her analysis was therefore in this case harmless.

"Synergism" and "Combination Patents"

Judge Boyle said "synergism" is "a symbolic reminder of what constitutes nonobviousness when a combination patent is at issue," and that under "either standard (*Graham* analysis or synergism) the combination ... simply lacks the unique essence of authentic contribution to the Teflon art which is the heart of invention."

A requirement for "synergism" or a "synergistic effect" is nowhere found in the statute, 35 U.S.C. When present, for example in a chemical case, synergism may point toward nonobviousness, but its absence has no place in evaluating the evidence on obviousness. The more objective findings suggested in *Graham,* supra, are drawn from the language of the statute and are fully adequate guides for evaluating the evidence relating to compliance with 35 U.S.C. § 103. *Bowser Inc. v. United States,* 388 F.2d 346, 181 Ct.Cl. 834, 156 USPQ 406 (Ct.Cl.1967). Judge Boyle treated synergism as an alternative considera-

tion. Hence the error of its analytical inclusion is harmless in view of Judge Boyle's employment of the *Graham* aids.

The reference to a "combination patent" is equally without support in the statute. There is no warrant for judicial classification of patents, whether into "combination" patents and some other unnamed and undefined class or otherwise. Nor is there warrant for differing treatment or consideration of patents based on a judicially devised label. Reference to "combination" patents is, moreover, meaningless. Virtually *all* patents are "combination patents," if by that label one intends to describe patents having claims to inventions formed of a combination of elements. It is difficult to visualize, at least in the mechanical-structural arts, a "non-combination" invention, i.e., an invention consisting of a *single* element. Such inventions, if they exist, are rare indeed. Again, however, Judge Boyle's inclusion in her analysis of a reference to the '087 patent as a "combination" patent was harmless in view of her application of *Graham* guidelines.

Similarly, Judge Boyle's reference to "the heart of invention" was here a harmless fall-back to the fruitless search for an inherently amorphous concept that was rendered unnecessary by the statute, 35 U.S.C. The *Graham* analysis here applied properly looked to *patentability,* not to "invention."

[4] We sit to review judgments, not opinions. The analysis reflected in an opinion filed with the judgment appealed from may on occasion be so flawed, however, as to obfuscate the true basis for the judgment or to establish that the judgment was erroneously based. Such might have here been the case if the judgment had not been accompanied by the alternative and proper analysis under *Graham* described above. In light of that alternative analysis, in which we see no error, we affirm the judgment declaring claims 1, 3, 4, 6, and 7 invalid for obviousness.

Infringement

When presented with patent validity and infringement issues, trial courts should, as Judge Boyle did here, decide both. First, the parties, witnesses and exhibits involved in both issues are before the court. If a judgment limited to one issue is reversed, it may become necessary to again call many of the same persons before the court for ***1541** trial or argument on the other. In any event, a remand would normally be necessary for a return by the trial court to whatever fact finding process may be involved in a determination of the undecided issue. Second, a finding that a claimed invention has or has not been appropriated by the alleged infringer may carry substantial weight in a court's analysis of *all* the evidence bearing on the obvious-nonobvious issue. An alleged infringer's lauding of all the available prior art may, for example, in some cases have a hollow ring when played against its disregard of that art and its copying of the invention.

The determination of non-infringement here was flawed by an unwarranted reading into the claims of that part of the specification devoted to a description of the "salt and pepper" process of making PTFE tubing. The "salt and pepper" process is set forth in no claim of the '087 patent. It is claimed in the separate patent described above. Whether Stratoflex employs a different process in forming its inner layer is irrelevant, the sole question being whether the accused tubing product of Stratoflex infringes the product claims of the '087 patent.

The error was harmless. Whether on proper analysis the Stratoflex "124" and "127" tubing products may be found to infringe claims 1, 3, 4, 6, and 7 need not be now determined. The claims having been found invalid, the issue has been rendered moot.

Conclusion

The judgment declaring claims 1, 3, 4, 6, and 7 invalid is affirmed.

AFFIRMED.

713 F.2d 1530, 218 U.S.P.Q. 871

Briefs and Other Related Documents (Back to top)

• 1983 WL 486722 (Appellate Brief) Reply Brief of Appellant (Apr. 22, 1983)Original Image of this Document (PDF)

• 1983 WL 486720 (Appellate Brief) Brief for Appellant (Feb. 14, 1983)Original Image of this Document (PDF)

• 1983 WL 486721 (Appellate Brief) Brief for Appellee (1983)Original Image of this Document (PDF)

END OF DOCUMENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jeffrey R. Dahlen, et al.

Title: USE OF B-TYPE NATRIURETIC PEPTIDE AS A PROGNOSTIC INDICATOR IN ACUTE CORONARY SYNDROMES

Appl. No.: 09/835,298

Filing Date: 4/13/2001

Examiner: Lam, Ann Y.

Art Unit: 1641

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below.

_____
(Printed Name)

_____
(Signature)

_____
(Date of Deposit)

DECLARATION OF DR. NORMAN ALAN PARADIS

I, Norman Alan Paradis, M.D., state and declare as follows:

1. I am currently Vice President of Clinical Medical Affairs for Biosite Incorporated, San Diego, CA, assignee of the above-referenced Dahlen *et al.* patent application. I am also a Visiting Professor of Surgery and Attending Physician at the University of Colorado Health Sciences Center, Denver Colorado. I received my medical degree from Northwestern University Medical School in 1984, and have been employed as a physician since that time. I have specialty training in Emergency Medicine, and have been a Fellow of the American Academy of Emergency Medicine since 1990. A copy of my *curriculum vitae* is attached to this declaration. I have read and am familiar with the above-referenced Dahlen *et al.* patent application and the Office Action dated July 27, 2006.

2. I have been asked to comment regarding the whether or not the discovery that BNP measurements (and measurement of BNP-related polypeptides such as NT-proBNP) provide independent prognostic information vis-à-vis "traditional" cardiac necrosis markers such as cardiac troponin across the full spectrum of acute coronary syndromes was unexpected at the

time the above-referenced Dahlen *et al.* patent application was filed, and whether that discovery is of practical significance.

3. I conclude that the independence of these measurements was important and unexpected, and of substantial practical experience. For convenience, I will refer to "BNP measurement" in the following comments, but these comments should be considered equally applicable to the measurement of BNP-related polypeptides such as NT-proBNP.

4. That the data in the present application demonstrating that BNP measurements are independent of cardiac necrosis markers such as cardiac troponin for prognosis is demonstrated by de Lemos *et al.*, *N. Engl. J. Med.* 345: 1014-21 (2001) (hereinafter "the deLemos *NEJM* paper"). The *NEJM* is considered by those of skill in the art to be perhaps the preeminent journal in the medical field, and publication in the *NEJM* is considered to be reserved for discoveries of the highest novelty and importance. I understand that the authors of the deLemos *NEJM* paper are investigators from the multicenter "TIMI-16" cardiovascular study that served as the source of samples for the examples in the patent application.

5. The surprising nature of the discovery that BNP as a prognostic marker is independent of what are considered "traditional" markers of cardiac necrosis such as cardiac troponins comes from a review of the scientific literature. With regard to cardiac troponin, Antman *et al.*, *N. Engl. J. Med.* 335: 1342-49, 1996 on page 1348, right column, states that cardiac troponin increases "presumably because the amount of myocardial necrosis increases." As for BNP, Hassan and co-workers reported in *Médecine Nucléaire* 24: 301-10, 2000, on the use of thallium-201 single photon emission computerized tomography (Tl-201 SPECT) to distinguish subjects having necrotic myocardium from subjects having ischemic myocardium. Hassan *et al.* then compared plasma BNP concentrations in these two groups, concluding that, while BNP was significantly increased in the case of cardiac necrosis, BNP did not increase due to cardiac ischemia. This would lead the skilled artisan to believe that BNP, like cardiac troponins, increases "presumably because the amount of myocardial necrosis increases." Thus, the skilled artisan would conclude that BNP would provide similar information to other necrosis markers such as troponin. The evidence provided in the present specification that this is not the case, then, was quite surprising.

6. Confirmation for my conclusion of the surprising nature of this discovery is provided by an editorial authored by the cardiologist LeRoy Rabbani, *N. Engl. J. Med.* 345: 1057-59 (2001), which was published in the same issue of the *NEJM* as the de Lemos *et al.* *NEJM* publication. The editorial discussed the de Lemos *et al.* article and specifically emphasized the importance of the discovery being reported (emphasis added):

> "[a] single measurement of B-type natriuretic peptide... predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, or unstable angina.... Moreover, the relation between the long-term risk of death and the B-type natriuretic peptide level was independent of electrocardiographic changes, troponin I levels, renal function, and the presence or absence of clinical evidence of congestive heart failure. Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

It is my understanding that companion editorials are generally reserved for extremely important findings. In addition, the *NEJM* editorial was authored by LeRoy Rabbani, an Associate Professor of Clinical Medicine at Columbia University, a highly experienced interventional cardiologist with over 20 years experience including an extensive bibliography (listed as an author on 47 articles in Medline). The fact that the de Lemos *et al. NEJM* article was accepted for publication, coupled with the companion *NEJM* editorial, is strong evidence that the findings in de Lemos are new and profound.

7. To understand the importance and unexpected nature of the discovery that BNP measurements provide independent prognostic information across the full spectrum of acute coronary syndromes ("ACS"), it is necessary to first understand the definition of "ACS," and the differences between myocardial infarction and myocardial ischemia. The term "acute coronary syndromes" is used as an umbrella term to refer to a spectrum of diseases – unstable angina ("UA"), non-ST-segment elevation myocardial infarction (NSTEMI), and myocardial infarction with ST-segment elevation (STEMI). Unstable angina refers generally to myocardial ischemia that causes pain at rest. In UA, the blockage of the affected artery does not completely block blood supply to the myocardium, and is not generally thought to result in the myocardial necrosis characteristic of myocardial infarction. Myocardial infarction, on the other hand, differs in that the blockage of the affected artery is sufficient to cause necrosis (that is, death) of myocardial

cells. *See, e.g.*, Alpert *et al., J. Am. Coll. Cardiol.* 36: 959-69, page 960, section entitled "II. Clinical Presentation" ("It is accepted that the term MI reflects a loss of cardiac myocytes (necrosis) caused by prolonged ischemia").

8. As discussed above, the Hassan *et al. Médecine Nucléaire* publication would lead the skilled artisan to believe that BNP, like cardiac troponins, increases "presumably because the amount of myocardial necrosis increases." Thus, it is plain that the skilled artisan would not have been led to believe that BNP would be a prognostic marker outside the context of myocardial infarction. Confirmation of the unexpected nature is provided by the fact that, once the relationship between BNP was discovered, it was published by the *New England Journal of Medicine*. Again, it is my understanding that publication in the *NEJM* is considered to be reserved for discoveries of the highest importance. And the import of the publication was such that the *NEJM* also elected to publish an accompanying editorial by the cardiologist LeRoy Rabbani, which highlighted the importance of the finding that "even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis."

9. Given the state of the art at the time the above-referenced Dahlen *et al.* patent application was filed, it is my conclusion that it was surprising and unexpected that BNP would be an independent prognostic marker relative to "traditional" cardiac necrosis markers like troponin. It was likewise surprising and unexpected that BNP would prove to be a prognostic marker across the entire spectrum acute coronary syndromes.

10. The practical result of the discovery is immediately apparent to those of skill in the art. That is, independent prognostic markers provide for improved patient risk stratification by providing complementary information to one another. Sabatine and his co-authors in *Circulation* 105: 1760-63, 2002, reports on the use of BNP, cardiac troponin I, and an inflammatory marker (C-reactive protein, or CRP) in a "multimarker strategy" for risk stratification of ACS patients. As the authors demonstrate, each of these markers can provide unique prognostic information in patients with ACS. The authors conclude that "[a] simple multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation allows risk stratification over a broad range of short- and long-term major cardiac

events." Sabatine *et al.*, Abstract. This practical advantage has been widely recognized, acknowledged, and adopted in the art, as demonstrated by the following excerpt from Silver *et al.*, "BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Disease," *CHF* 10[5 Suppl. 3]: 1-30 (2004). In this report, prepared by "an expert panel... gathered by selecting clinicians and scientists with expertise with the natriuretic peptide system," the practical advantage of combined measurements of BNP and cardiac troponin is made clear:

> 7.2 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Multimarker panels that include BNP troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Oct 18, 2006
Date

Norman Alan Paradis, M.D.

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 16

Filed by: Trial Section Merits Panel
Mail Stop Interference
P.O. Box 1450
Alexandria, VA 22313-1450
Tel: 571-272-9797
Fax: 571-273-0042

Filed
18 May 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES
(Administrative Patent Judge Sally Gardner Lane)

FAXED

MAY 18 2005

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

ERIC B. **STANTON**,
and GEORGE JACKOWSKI

Junior Party,
(Patent 6,461,828),

v.

JEFFREY R. **DAHLEN**,
GUNARS E. VALKIRS, and KENNETH F. BUECHLER

Senior Party,
(Application 09/835,298).

Patent Interference No. 105,167

Before McKelvey, Senior Administrative Patent Judge, and Lorin and Lane, Administrative Patent Judges.

Lane, Administrative Patent Judge.

Judgment - Request for Adverse - Bd.R. 127(b)

Stanton has filed a paper requesting that judgment be entered against it. (Paper 113 at 2).

Upon consideration of the record and for reasons given, it is

ORDERED that judgment on priority as to Count 1, the sole count of the interference, is entered against junior party ERIC B. STANTON and GEORGE JACKOWSKI;

FURTHER ORDERED that junior party ERIC B. STANTON and GEORGE JACKOWSKI is not entitled to a patent containing claims 1-5 of patent 6,461,828, which claims correspond to Count 1 (Paper 1 at 5 and Paper 106 at 1) ; and

FURTHER ORDERED that a copy of this judgment shall be given a paper number and entered into the administrative records of Stanton's 6,461,828 patent and Dahlen's 09/835,298 application.

18 May 2005
Alexandria, VA

cc (via facsimile and first class mail):

Attorney for **STANTON**:

Michael A. Slavin, Esq.
McHALE & SLAVIN, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410

Fax: 561-625-6572

Attorney for **DAHLEN**:

George E. Quillin, Esq.
FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, DC 20007-5109

Fax: 202-672-5399

INTERFERENCE DIGEST

Interference No. 105,167 Paper No. 14

Name: Eric B. Stanton et al.

Serial No.: 09/946,171 Patent No. 6,461,828, granted 10/08/02

Title: Conjunctive analysis of biological marker expression for diagnosing organ failure

Filed: 09/04/01

Interference with Dahlen et al.

DECISION ON MOTIONS

Administrative Patent Judge,_____ Dated,_____

FINAL DECISION

Board of Patent Appeals and Interferences, Adverse Dated, 5/18/05

Court,_____ Dated,_____

REMARKS

This should be placed in each application or patent involved in interference in addition to the interference letters.

The opinion in support of the decision being entered today
is not binding precedent of the Board

Paper 105

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ERIC B. STANTON and GEORGE JACKOWSKI
Junior Party,
(Patent 6,461,828)
v.

JEFFREY R. DAHLEN, GUNARS E. VALKIRS,
and KENNETH F. BUECHLER
Senior Party
(Application 09/835,298)

Patent Interference Nos. 105,167

ORDER

Before: McKELVEY, Senior Administrative Patent Judge, and LORIN and LANE, Administrative Patent Judges.

LORIN, Administrative Patent Judge

Upon consideration of the record, it is ORDERED that:

- Claim 2 of Stanton's interfering patent US 6,461,828, which is currently designated as not corresponding to Count 1, is designated as corresponding to the count.
- Stanton Preliminary Motions 1-4 are denied.

- Dahlen Preliminary Motions 1-2 are denied.
- Dahlen Preliminary Motion 3 is granted.
- Dahlen Motions 4-6 are dismissed.

An opinion explaining the basis for our decision shall follow.

FURTHER ORDERED that the parties may wish to pursue settlement of this interference along the lines mentioned at oral argument.

FURTHER ORDERED that the parties not respond to this order with a request for rehearing. Such a request, if necessary, should wait until after the parties have reviewed a forthcoming Decision on Motions, wherein we will fully explain our reasoning. See Bd.R. 125(c)(1)

FRED E. McKELVEY
Senior Administrative Patent Judge

HUBERT C. LORIN
Administrative Patent Judge

SALLY GARDNER LANE
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

Interference No. 105,167

cc (via facsimile and first class mail):

Counsel for STANTON:

Michael A. Slavin, Esq.
McHALE & SLAVIN, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410

Fax: 561-625-6572

Counsel for DAHLEN:

George E. Quillin, Esq.
FOLEY & LARDNER LLP
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109

Fax: 202-672-5399

Paper 106

Filed by: Sally Gardner Lane
Administrative Patent Judge
Mail Stop Interference
P.O. Box 1450
Alexandria VA 22313-1450
Tel: 571-272-9797
Fax: 571-273-0042

Filed
9 March 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ERIC B. STANTON,
and GEORGE JACKOWSKI

Junior Party,
(Patent 6,461,828),

v.

JEFFREY R. DAHLEN,
GUNARS E. VALKIRS, and KENNETH F. BUECHLER

Senior Party,
(Application 09/835,298).

Patent Interference No. 105,167

Before GARDNER LANE, Administrative Patent Judge.

REDECLARATION - Bd.R. 203(c)

Upon consideration of the record, it is

ORDERED that the interference is redeclared to the following extent only:

Claim 2 of Stanton involved patent, 6,461,828, is designated as corresponding to Count 1;

FURTHER ORDERED that the attached Standing Order shall be in effect for the remainder of the interference; and

FURTHER ORDERED that all time periods set in the interference remain in effect.

Enc: Standing Order

cc (via facsimile and first class mail):

Attorney for STANTON: (real party in interest: Nanogen.)

Michael A. Slavin, Esq.
MICHAEL & SLAVIN, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410

Fax: 561-625-6572

Attorney for DAHLEN (real party in interest: Biosite, Inc.):

George E. Quillin, Esq.
FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, DC 20007-5109

Fax: 202-672-5399

Paper 107

Filed by: Sally Gardner Lane
Administrative Patent Judge
Mail Stop Interference
P.O. Box 1450
Alexandria VA 22313-1450
Tel: 571-272-9797
Fax: 571-273-0042

Filed
9 March 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ERIC B. **STANTON**,
and GEORGE JACKOWSKI

Junior Party,
(Patent 6,461,828),

v.

JEFFREY R. **DAHLEN**,
GUNARS E. VALKIRS, and KENNETH F. BUECHLER

Senior Party,
(Application 09/835,298).

Patent Interference No. 105,167

Before GARDNER LANE, Administrative Patent Judge.

ORDER - RULE 123(a)
(Times for priority motions)

The TIME PERIODS described below are set out in an Appendix to this ORDER. Action specified for each TIME PERIOD must be completed by the date specified for the TIME PERIOD.

The parties are authorized to stipulate different times (earlier or later, but not later than TIME PERIOD 15) for TIME PERIODS 9 through 14.[1] A notice of the stipulation must be promptly filed. The notice must be in the form of a photocopy of the Appendix attached to this ORDER with old dates crossed out and new dates inserted by hand. The parties may not stipulate an extension of TIME PERIODS 15 or 16.

1. **TIME PERIOD 11**

The junior party must:

a. File and serve a motion on priority and

b. Serve but not file evidence in support of the junior party priority case.

If the junior party does not file a priority motion, the junior party must arrange a conference call to the administrative patent judge so that appropriate action may be taken.

2. **TIME PERIOD 12**

The senior party must:

a. File and serve a motion on of priority and

b. Serve but not file evidence in support of the senior party priority case.

[1] In stipulating different times, the parties should consider the effect of the stipulation on times (1) to object to evidence (5 business days, Bd. R. 155(b)(1)), (2) to supplement evidence (10 business days, Bd. R. 155(b)(1)), (3) to begin cross-examination (no earlier than 21 days after service, SO ¶ 22.1.1) and (4) to conclude cross examination (at least 10 days before opposition or reply is due, SO ¶ 22.1.2).

3. **TIME PERIOD 13**

   a. File and serve oppositions to all priority motions and

   b. Serve but do not file evidence in support of these oppositions.

4. **TIME PERIOD 14**

   a. File and serve replies to all oppositions and

   b. Serve but do not file evidence in support of these replies.

5. **TIME PERIOD 15**

   a. File and serve any request for oral argument on priority,

   b. File and serve motions to exclude evidence (Bd. R. 155(c); SO ¶ 21.3),

   c. File and serve observations on cross examination (SO ¶ 22.7) of reply testimony, and

   d. File and serve a list of any issues other than priority that should be considered in rendering a final decision in the interference.[2]

6. **TIME PERIOD 16**

   a. File and serve oppositions to an opponent's motion to exclude evidence and

   b. File and serve any response to observations.

---

[2] There is no need to list an issue previously resolved by a decision entered by a panel of at least three administrative patent judges inasmuch as these decisions merge with the judgment when a final decision is entered.

7. **TIME PERIOD 17**

File and serve replies to oppositions to motions to exclude evidence.

Deposition transcripts

Transcripts of cross examinations and depositions taken under 35 U.S.C. § 24 must be served, but not filed with the board until the exhibits are filed.

Serving priority exhibits

An exhibit, including an affidavit, relied upon in connection with priority must be served but not filed with the motion, opposition, reply or affidavit in which the exhibit is first mentioned.

TIME PERIOD 18: Filing the priority record

1. File original set of your exhibits and one copy (or three copies if oral argument is set) of your exhibits;
2. For your priority motion, file one folder (three folders if an oral argument is set each) containing a set of motion documents consisting of:
   a. The priority motion,
   b. Any corresponding opposition,
   c. Any corresponding reply,
   d. Any corresponding observations, and
   e. Any corresponding response to the observations.
3. File any ZIP® 100 Mb disk or CD-ROM.

Revised 13 September 2004

cc (via facsimile and first class mail):

Attorney for STANTON: (real party in interest: Nanogen.)

Michael A. Slavin, Esq.
MICHAEL & SLAVIN, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410

Fax: 561-625-6572

Attorney for DAHLEN (real party in interest: Biosite, Inc.):

George E. Quillin, Esq.
FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, DC 20007-5109

Fax: 202-672-5399

Appendix--ORDER - RULE 123(a)
(Times for priority motions)

Interference 105,167

TIME PERIOD 11 ..... **21 April 2005**
Junior party only file priority brief and serve
(but do not file) priority evidence

TIME PERIOD 12 ..... **2 June 2005**
Senior party only file priority brief and serve
(but do not file) priority evidence

TIME PERIOD 13 ..... **8 July 2005**
File opposition to priority briefs
Serve (but do not file) opposition evidence

TIME PERIOD 14 ..... **19 August 2005**
File reply
Serve (but do not file) reply evidence

TIME PERIOD 15 ..... **29 September 2005**
Request hearing
File list of issues to be considered
File observations
File motion to exclude

TIME PERIOD 16 ..... **20 October 2005**
File response to observations
File opposition to motion to exclude

TIME PERIOD 17 ..... **3 November 2005**
File reply to opposition to motion to exclude

TIME PERIOD 18 ..... **10 November 2005**
File and serve exhibits
File sets of priority motions
File ZIP® disks and CD-ROMs